PI: **Abel, Taylor John**	Title: Flexible representation of speech in the supratemporal plane.	
Received: 07/15/2020	Opportunity: PA-20-196	Council: 01/2021
Competition ID: FORMS-F	FOA Title: NIH Exploratory/Developmental Research Grant Program (Parent R21 Basic Experimental Studies with Humans Required)	
1R21DC019217-01A1	Dual:	Accession Number: 4471894
IPF: 2059802	Organization: [redacted]	
Former Number: 1R21DC019217-01	Department: Neurological Surgery	
IRG/SRG: LCOM	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: [redacted] [redacted] [redacted]	Animals: N Humans: Y Clinical Trial: Y Current HS Code: 30 HESC: N HFT: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Taylor Abel MD	[redacted]	PD/PI
Lori Holt PhD	[redacted]	MPI

OMB Number: 4040-0010
Expiration Date: 12/31/2022

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
DC019217

b. Agency Routing Number

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** [redacted]

Legal Name*: [redacted]
Department: Office of Sponsored Programs
Division:
Street1*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Jennifer Middle Name: E. Last Name*: Woodward Suffix: PhD
Position/Title: Vice Chancellor for Sponsored Programs
Street1*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
[redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* X: Other (specify)

Other (Specify): Private, non-profit, state-related, educ inst
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Flexible representation of speech in the supratemporal plane.

12. PROPOSED PROJECT
Start Date* Ending Date*
04/01/2021 03/31/2023

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Taylor Middle Name: Last Name*: Abel Suffix: MD

Position/Title: Assistant Professor

Organization Name*: [redacted]

Department: Neurological Surgery

Division: School of Medicine

Street1*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

[redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Jennifer Middle Name: E. Last Name*: Woodward Suffix: PhD

Position/Title*: Vice Chancellor for Sponsored Programs

Organization Name*: University of Pittsburgh

Department: Office of Sponsored Programs

Division:

Street1*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*

Jennifer.Woodward

Date Signed*

07/15/2020

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:2020_NIH_R21_PerceptualWeights_CoverLetter_fin.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 12/31/2022

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

[redacted]

Additional Location(s)

File Name:

Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number 00006790

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	2020_NIH_R21_PerceptualWeights_ProjectSummary_.pdf
8. Project Narrative*	2020_NIH_R21_PerceptualWeights_ProjectNarrativ.pdf
9. Bibliography & References Cited	2020_NIH_R21_PerceptualWeights_References_fina.pdf
10.Facilities & Other Resources	2020_NIH_R21_PerceptualWeights_Resources_final.pdf
11.Equipment	2020_NIH_R21_PerceptualWeights_Equipment_final.pdf

Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

PROJECT SUMMARY

Speech communication plays a crucial role in conveying our thoughts to others, maintaining social ties, and supporting educational achievement. As a result, communication disorders that impact speech perception like autism, dyslexia, and hearing loss can be costly to both individuals and society. Understanding the neurobiological bases of speech processing is an important goal that has been hastened by invasive intracranial electrophysiology in neurosurgical contexts. Yet, substantial behavioral evidence demonstrates dynamic, flexible aspects of the mapping of speech input to phonemes that is not yet accounted for in neurobiological models. This Exploratory/Developmental R21 project pursues the central hypothesis that listening context systematically impacts cortical response to speech and therefore affects the diagnosticity of acoustic dimensions in signaling phonemes. A newly established cross-disciplinary research team will use intracerebral recording via stereoelectroencephalography (sEEG) obtained in a neurosurgical context to pursue this hypothesis. Like electrocorticography (ECoG), sEEG offers high spatiotemporal resolution and can target the cortical surface, including superior temporal gyrus (STG). Owing to the intracortical electrode placement, sEEG electrodes record through the supratemporal plane, specifically targeting both deep sulcal and gyral grey matter including superior temporal sulcus (STS) and Heschl's gyrus (HG). Simultaneous scalp electroencephalography (EEG) will be acquired to link these intracortical measures with noninvasive approaches appropriate in studies of healthy listeners. Aim 1 will establish neural response to two acoustic-phonetic dimensions as a function of the *perceptual weight* with which they signal phoneme identity. This will provide a baseline response for each participant for comparison as experimental manipulations to listening context shift perceptual weights in Aim 2, and will establish how individual differences in perceptual weighting strategies predict cortical electrophysiological response. Aim 2 will introduce two well-established manipulations that, behaviorally, shift perceptual weights relative to baseline: introduction of noise and introduction of an 'accent' for which the short-term speech input deviates from distributional regularities of the native language. Examination of experimental manipulations within-participant will provide a sensitive means by which to assay changes in neural response as a function of changes in perceptual weights arising across listening contexts. Participants will be sampled across later adolescence (15-25 years), a period during which perceptual weights provide informative heterogeneity. The project will compound its impact by filling an important gap in understanding of speech processing, building a bridge from invasive electrophysiological studies with patients to scalp EEG measures of human listeners through combined sEEG+EEG, wedding classic and state-of-the-art computational approaches to inform mechanisms, and delivering an understanding of the dynamic, flexible nature of speech processing with substantial implications for communication disorders.

PROJECT NARRATIVE

The goal of this research is to discover the fundamental mechanisms that support listeners' ability to flexibly perceive speech even as listening contexts change to include foreign accents or background noise. An understanding of how speech perception flexibly adapts will have important implications for developing new rehabilitative strategies for communication disorders like aphasia, dyslexia and autism that impact speech perception.

FACILITIES & OTHER RESOURCES

Laboratory

Children's Hospital of Pittsburgh (CHP) provides a child-friendly environment that is ideal for care of pediatric patients and pediatric clinical / translational research. CHP has a fully equipped 8-bed epilepsy-monitoring unit (EMU) where intracranial electrophysiology experiments will take place. CHP has a neuroimaging research facility equipped with a 3T Siemens MR scanner. All data acquisition from patient populations will take place at CHP.

- **Magnetic Resonance Imaging Room:** CHP has a Siemens 3 Tesla MR scanner available for research. The magnet rooms are magnetically, acoustically, and RF shielded.
- **MRI Simulator:** CHP has an MRI simulator that mimics the scanner room both in appearance and noise. This serves to acclimate research participants to the scanner environment. A stimulus presentation system similar to the one used in the scanning environment has been installed in the simulator for training children on experimental tasks.

Animal: None

Office: PI Abel has a closed-door laboratory space in the basement of CHP that provides direct elevator access to the EMU for quick transport of research electrophysiology equipment (via cart). Additionally, within the Division of Neurosurgery at CHP, the PI's lab has four cubicles equipped with computers that are allocated for his research team (currently a postdoctoral fellow, a research assistant, and two medical students). PI Abel also has his own clinical office with a computer that is on the same floor and in close proximity to laboratory research cubicles.

PI Abel hosts weekly lab meetings in a conference room on the same floor as his office and research cubicles. This conference room is equipped with a white board and projector to facilitate data presentations.

PI Holt has offices a short distance from CHP, on the [redacted] University campus. These rooms have designated space for files, manuscript preparation, and overall organizational duties. The offices are equipped with locking file cabinets, a desk, a computer equipped with all the software available on laboratory computers, a telephone, and a printer to perform these functions.

PI Holt hosts weekly lab meetings in a conference room in the same building as the offices. This room has presentation equipment, white boards, a projector and videoconferencing equipment.

Other:

Scientific and Intellectual Environment

There is a vibrant, highly collaborative intellectual environment at the [redacted] area available to the PI, Co-I, and personnel. The University of Pittsburgh is ranked 5th among US schools in NIH funding and 1st in National Institute of Mental Health funding. Additionally, the [redacted] has the Clinical and Translational Science Institute which helps researchers develop and execute innovative programs. It benefits from being immediately adjacent to Carnegie Mellon University, the academic home of PI Holt.

Children's Hospital of Pittsburgh: Patient recruitment and patient electrophysiology experiments will take place at the at Children's Hospital [redacted] As a world-class academic children's hospital ranked in the top 10 for NIH funding among children's hospitals and in the top 10 by US World and News for children's hospital.

Department of Psychology, Carnegie Mellon University: PI Holt has a laboratory at Carnegie Mellon University, a short bus ride or drive from Children's Hospital [redacted] Her laboratory is suitable to accommodate pilot testing and paradigm development and provides ample resources to support the development of the graduate student trainee.

Neuroscience Institute, Carnegie Mellon University: PI Holt is affiliated with the Neuroscience Institute of Carnegie Mellon University (https://www.cmu.edu/ni/), which provides resources to support collaborative neuroscience endeavors across academic departments and centers.

Department of Otolaryngology: The PIs are affiliated with the Pittsburgh Hearing Research Center (PHRC http://www.phrc.pitt.edu/), based within the Department of Otolaryngology. The PHRC focuses on the interdisciplinary study of basic and clinical aspects of hearing and sound perception, in health and disease. The PHRC includes members from different Medical School, School of Health and Rehabilitation Sciences, and Arts and Sciences Departments [redacted] as well as faculty from Carnegie Mellon University. The mission of these centers is to facilitate interdisciplinary research to provide data-driven knowledge to physicians and patients and to offer treatments.

Department of Neurobiology: The department of Neurobiology currently has a T32 that supports two predoctoral and two postdoctoral trainees per year. The focus of this T32 is auditory and vestibular neuroscience. Fellows receive training in a wide range of neuroscience methodologies (cell level to systems level) and education in clinical populations. PI Holt is a preceptor on this training grant.

Behavioral-Brain Training Program: PI Holt is co-Director of a T32 predoctoral training program supporting 8 trainees/year at Carnegie Mellon University and [redacted] This training program supports students working at the interface of brain and behavior. This program offers hands-on experiences with different neuroscience methods and technology and training from an interdisciplinary group of preceptors.

Center for the Neural Bases of Cognition (CNBC http://www.cnbc.cmu.edu/): The CNBC, an inter-institutional center that leverages the complementary strengths of the [redacted] (in basic and applied neuroscience) and Carnegie Mellon in cognitive and computational neuroscience. The CNBC fosters cross-university research and education (affiliates can train and take coursework at both Universities) with experience using state-of-the-art functional neuroimaging technology, access to human and animal populations and research facilities. In addition to excellent resources, the center has a successful record of getting training grants that attract strong predoctoral and postdoctoral applicants. The postdoctoral associate and graduate student associated with this project will be associated with the CNBC.

EQUIPMENT

Children's Hospital of Pittsburgh (CHP) provides a child-friendly environment that is ideal for care of pediatric patients and pediatric clinical / translational research. CHP has a fully equipped 8-bed epilepsy-monitoring unit (EMU) where intracranial electrophysiology experiments will take place. CHP has a neuroimaging research facility equipped with a 3T Siemens MR scanner. All data acquisition from patient populations will take place at CHP. CHP is a facility equipped to conduct cutting-edge clinical research in a medical facility, including with patient populations. CHP has the following equipment available for use by the MPIs:

- **Magnetic Resonance Imaging System:** CHP has a Siemens 3 Tesla MR scanner available for research. There is associated instrumentation to handle high rates of storage required by fMRI scanning. The magnet rooms are magnetically, acoustically, and RF shielded. The research MR at CHP has administrative and technical support, including MR physicists who continually monitor and optimize the functioning of the MR scanners. Staff physicists and radiologists are also available for the development of new pulse sequences tailored to the needs of the individual investigator. The scanner has an integrated stimulus delivery system that has been installed for the presentation of stimuli and the detection of responses in the fMRI environment on each scanner. The MR scanner is also equipped with an eye tracker.
- **Electrophysiology Recording System:** Nomad (Ripple, Inc., Salt Lake City, UT) 512-channel Neural Interface Processor (30kHz sampling rate), Grapevine touchproof adaptors (4), Grapevine digital I/O, Grapevine analogue I/O, and head stages (4); handgrip force transducers (2) and associate software and hardware (MIE medical research ltd., Leeds, UK).
- **Eye Tracking:** EyeLink Portable Duo eye tracking system (SR Research, Ottawa, Ontario, Canada), with sampling rates of 2,000 Hz (head-stabilized mode) or 1,000 Hz (free-to-move mode). Experiment Builder and Data Viewer software (SR Research, Ottawa, Ontario, Canada).
- **Computing:** All laboratory personnel have a personal computer. All computers are networked and have access to a laser printer. Analysis computers will be integrated with the Pittsburgh Supercomputing Center (PSC). All computers are password-protected, with data backed up daily.
- **Software:** Investigators have access to MATLAB mathematical analysis software (MATLAB, The Mathworks, Inc., Natick, MA); JupyterHub server for Python development (Jupyter, Worldwide). Offline Sorter software (Plexon, Inc., Dallas, Texas); Microsoft SQL Server 2012 (Microsoft, Inc., Redmond, WA); R (R Foundation for Statistical Computing, Vienna, Austria). FreeSurfer MRI imaging analysis software (FreeSurfer, The General Hospital Corporation, Boston, MA, USA). MRIcron cross-platform NIfTI format image viewing software (Neuropsychology Lab, University of South Carolina, Columbia, SC, USA). Brainstorm neuroimage recording analysis software (Biomedical Imaging Group, University of South Carolina, Columbia, SC, USA).
- **Data Storage:** Combined computational and storage machine; storage includes three 10 TB hard drives in RAID 5 configuration (20 TB effective storage, single drive fault tolerance) and remote backup for triply redundant storage. Liquid-cooled Intel Core i9-9900K CPU with 16 MB cache (3.6 GHz, 8 physical cores, 16 threads). 64 GB HyperX DDR4 RAM at 2800/3000 MHz. 2 NVLinked Nvidia Titan RTX CUDA-enabled graphics cards, totaling 48 GB VRAM. 2 TB Samsung 970 EVO M.2 solid-state hard drive for I/O-intensive operations. Laptop computers.

Carnegie Mellon University's Pittsburgh Cognitive Auditory Neuroscience (PCAN) research laboratories, under the direction of Dr. Holt, provide full access to state-of-the-art acoustic recording, signal processing, and auditory experimentation facilities including sound-isolating booths. Though data collection will take place through CHP, the project will have full access to the resources of Dr. Holt's CMU laboratory.

OMB Number: 4040-0010
Expiration Date: 12/31/2022

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Taylor Middle Name Last Name*: Abel Suffix: MD

Position/Title*: [redacted]

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: [redacted]

Phone Number*: 412-692-8142 Fax Number:

E-Mail*: abelt@pitt.edu

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD Degree Year: 2010

Attach Biographical Sketch*: File Name: 2020_NIH_R21_PerceptualWeights_Biosketch_ABEL_.pdf

Attach Current & Pending Support: File Name:

Funding Opportunity Number: PA-20-196 . Received Date: 2020-07-15T15:11:48.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: Lori Middle Name Last Name*: Holt Suffix: PhD

Position/Title*: Professor
Organization Name*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 1999

Attach Biographical Sketch*: File Name: 2020_NIH_R21_PerceptualWeights_Biosketch_HOLT_.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Taylor John Abel

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor of Neurological Surgery

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Washington, Seattle WA	B.S.	6/2004	Neurobiology
University of Washington, Seattle WA	M.D.	6/2010	Medicine
University of Iowa, Iowa City IA	Residency	6/2016	Neurosurgery
University of Iowa, Iowa City IA	Postdoctoral	6/2015	Cognitive Neuroscience
CHU de Grenoble, France	Fellow	6/2017	Epilepsy Surgery
The Hospital for Sick Children, Toronto, Canada	Fellow	6/2018	Pediatric Neurosurgery

A. Personal Statement

I am an Assistant Professor of Neurological Surgery at the University of Pittsburgh, a pediatric neurosurgeon, and Surgical Director of the Pediatric Epilepsy Surgery Program at UPMC Children's Hospital of Pittsburgh (CHP). I direct the Pediatric Brain Electrophysiological Laboratory (PBEL) at CHP. The goals of this project are to use human sEEG and EEG recordings to understand flexible speech representation in adolescent auditory cortex in neurosurgery patients. I have the experience, skills, and expertise necessary to successfully perform this multi-disciplinary and multi-institutional collaborative research project. This will be supported, as well, by the geographic proximity and intellectual engagement of collaborators spanning auditory cognitive neuroscience and speech communication who have essential domain expertise and also bring project management expertise. My background and training are in pediatric neurosurgery, epilepsy surgery, and human brain neurophysiology. In my role, I work with my colleagues to design and perform experiments and to publish our work in the peer-reviewed literature. I have access to departmental and institutional resources sufficient to ensure that the needs of the PBEL and our research collaboration are met. My research laboratory offers the equipment and facilities necessary to conduct the clinical aims of the proposed research. The combination of investigators and specialized research capabilities of the PBEL and the Pittsburgh Cognitive Auditory Neuroscience group are uniquely suited to pursue the scientific aims of this application.

B. Positions and Honors

Positions and Employment:

2010 – 2016 Intern, Resident, Chief Resident, Neurological Surgery, University of Iowa
2013 – 2015 Postdoctoral Fellow, Human Brain Research Laboratory and Benton Neuropsychology Laboratory, University of Iowa (Mentors: Dan Tranel and Matthew Howard, III)
2016 - 2017 Fellow Associate, Neurological Surgery, University of Iowa
2017 Clinical Fellow, Epilepsy and Functional Neurosurgery, CHU Grenoble
2017 – 2018 Robin and Judith Humphreys Fellow (Chief Fellow) in Pediatric Neurosurgery, The Hospital for Sick Children and University of Toronto
2018 - Assistant Professor of Neurological Surgery, University of Pittsburgh
2018 - Surgical Director, Pediatric Epilepsy Surgery Program, UPMC Children's Hospital of Pittsburgh
2019 - Adjunct Faculty, Department of Bioengineering, University of Pittsburgh

Other Experience and Professional Memberships:

2010 – 2018 Member, Congress of Neurological Surgeons
2010 - Member, American Association of Neurological Surgeons
2013 – 2016 Member, American Society of Functional and Stereotactic Neurosurgery
2014 - Member; Membership Committee (2016 – present), American Epilepsy Society
2014 - Member; North American Regional Representative, ILAE Young Epilepsy Section (2018 -); Ex-Officio Member of Executive Board of ILAE North America (2018 -); ILAE Young Epilepsy Section Executive Board (2018 -); Task Force on Research Advocacy and Priorities (2019 -), International League Against Epilepsy
2017 - Member; Clinical Guideline Committee (2019 – present), AANS / CNS Joint Section on Pediatric Neurosurgery
2018 - Member, Flux Society for Developmental Cognition Neuroscience
2018 - Member, Society for Neuroscience
2019 - Neurosurgery Representative, University of Pittsburgh Institutional Review Board (IRB)

Honors

2005 Mary Gates Research Scholar, University of Washington
2007 Medical Student Research Training Award, University of Washington School of Medicine
2009 Functional Neurosurgery Top Ten Abstract, Congress of Neurological Surgeons
2010 Third Place Abstract, Functional and Stereotactic Neurosurgery, AANS
2014 American Epilepsy Society Fellow Travel Award
2014 NIH Loan Repayment Award (Clinical Science)
2014 NIH Ruth L. Kirschstein National Research Service Award
2014 Stereotactic and Functional Neurosurgery Resident Award, Congress of Neurological Surgeons
2014 First Place Abstract, Iowa Medical Society
2016 NIH Loan Repayment Award Renewal
2017 Robin and Judith Humphreys Fellow in Pediatric Neurosurgery

C. Contributions to Science

H-index: 15**, Citations:** 725
Google Scholar Profile: https://scholar.google.com/citations?user=1cBCgOIAAAAJ&hl=en

1. Cortical physiology of auditory and visual convergence for person and object identification in the human anterior temporal lobe (ATL). I have a long-standing interest in understanding the neural mechanisms of person and object identification in the human temporal lobe, particularly the anterior temporal regions. Lesions studies show that damage to the ATL is associated with impaired visual and auditory naming of people, places, and things. I conducted work to describe the large-scale physiologic mechanisms associated with visual and auditory naming in the human ATL. First, in collaboration with Dr. Hiroto Kawasaki and Dr. Matthew Howard, we developed a specialized electrode array that provides dense coverage of the ATL in epilepsy surgery patients. Using this array, I described convergent beta band responses to voice and face identification in the human ATL. I further demonstrated that these beta band responses occur regardless of ATL laterality and uniqueness of stimulus being identified. In collaboration with Dr. Chris Petov, we developed a model of person and object-identification in the primate and human brain that involves multisensory convergence and amodal cortical representation in the superior temporal sulcus (STS). I am continuing this work now examining neural mechanisms of speaker identification in the human STS.

a. **Abel TJ**, Rhone A, Nourski KV, Granner MA, Oya H, Tranel DT, Kawasaki H, Howard MA III. Electrodcorticographic monitoring of the temporal pole with a specialized electrode array: technique and preliminary results. *Physiol Meas,* Mar 35(3): 323-37, 2014.
b. **Abel TJ**, Rhone AE, Nourski NV, Kawasaki H, Oya H, Griffiths TD, Howard III, MA, Tranel D. Direct physiologic evidence of a heteromodal convergence region for proper naming in the human left anterior temporal lobe. *J Neurosci* 35(4): 1513 – 1520, 2015
c. **Abel TJ**, Rhone AE, Nourski KV, Howard III MA, Tranel D. Investigating the anterior temporal lobe with direct intracranial recordings. *Neurosurgery* 62 (suppl 1): 185 – 9, 2015.

d. Perrodin C, Kayser C, **Abel TJ,** Logothetis NK, Petkov CI. Who is that? Brain Networks and Mechanisms for Identifying Individuals. Trends Cogn Sci. 19 (12):783-96, 2015.
e. **Abel TJ**, Rhone AE, Nourski KV, Ando TK, Oya H, Kovach CK, Kawasaki H, Howard III MA, Tranel D. Beta modulation reflects name retrieval in the human anterior temporal lobe: An intracranial recording study. *J Neurophysiol*, April 16, 2016.

2. Clinical outcomes of stereoelectroencephalography (sEEG), subdural grids (SDE), and other invasive monitoring methods in epilepsy surgery. An ongoing research interest of mine is to understand the safest and most effective methods for invasive recording in epilepsy surgery patients. Approximately 50% of epilepsy surgery patients require invasive monitoring to localize the epileptic focus, but the optimal technique (i.e. sEEG or SDE) remains unknown. We recently published the largest systematic review comparing clinical outcomes of sEEG and SDE, which suggests that sEEG is associated with higher rates of post-resection seizure freedom and lower rates of invasive monitoring morbidity. I have also published results of sEEG clinical outcomes in pediatric patients. The relatively efficacy of sEEG and SDE continues to be a matter of debate, which I plan to continuing exploring in my clinical research studies.

a. Remick M, Ibrahim GM, Mansouri A, Abel TJ. Patient phenotypes and clinical outcomes in invasive monitoring for epilepsy: An individual patient data meta-analysis. Epilepsy & Behavior. 2020 Jan 1;102:106652.
b. Yan H, Katz JS, Anderson M, Mansouri A, Remick M, Ibrahim GM, **Abel TJ**. Method of invasive monitoring in epilepsy surgery and seizure freedom and morbidity: A systematic review. Epilepsia. 2019 Sep;60(9):1960-1972.
b. Katz JS, **Abel TJ**. Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence? Neurotherapeutics. 2019 Jan;16(1):59-66.
c. **Abel TJ,** Varela Osorio R, Amorim-Leite R, Mathieu F, Kahane P, Minotti L, Hoffmann D, Chabardes S. Frameless robot-assisted stereoelectroencephalography in children: technical aspects and comparison with Talairach frame technique. J Neurosurg Pediatr. 2018 Jul;22(1):37-46.
e. **Abel TJ,** Woodroffe RW, Moritani T, Capizzano A, Kirby P, Howard MA III, Kawasaki H, Werz MA. The Role of the Temporal Pole in Temporal Lobe Seizure Networks: An Intracranial Electrode Investigation. Oct 13: 1-9, *J Neurosurg, 2017*

3. The role of ventromedial prefrontal cortex (vmPFC) in value based decision-making, personality, and quality of life in neurosurgery patients. Using a combination of lesion mapping techniques and experimental neuropsychology, I have examined the role of vmPFC lesions in impairment to decision making and personality disturbance in neurosurgical patients. Specifically, we investigated patients with olfactory groove meningioma who often present with subjective complaints of personality change and often have impairments in adaptive functioning out of proportion to the impairment measured by routine neuropsychological testing. We showed that patients with meningioma lesions involving the vmPFC have impairment in both adaptive functioning and value based decision-making (as measured by the Iowa Gambling Task), while patients with meningioma lesions in other brain areas do not exhibit these characteristics. We further showed that personality disturbance as measured by the Iowa Scales of Personality Change (ISPC) is associated with impairment in adaptive functioning. I have also investigated surgical lesions of the vmPFC in children who have undergone epilepsy surgery.

a. **Abel** TJ, Manzel K, Bruss J, Belfi AM, Howard MA 3rd, Tranel D. The cognitive and behavioral effects of meningioma lesions involving the ventromedial prefrontal cortex. J Neurosurg. 2016 Jun;124(6):1568-77.
b. Barrash J, **Abel TJ**, Okerstrom-Jezewski K, Zanaty M, Manzel K, Bruss J, Howard MA 3rd, Tranel D. Acquired personality disturbances after meningioma resection are strongly associated with impaired quality of life. In Press, Neurosurgery.
c. Stewart E, **Abel TJ**, Davidson B, Smith ML. Behaviour outcomes in children with epilepsy 1 year after surgical resection of the ventromedial prefrontal cortex. Neuropsychologia. 2019 Aug 6;133:107155.
d. **Abel TJ**, Barrash J, Tranel D. Letter to the Editor. Neuropsychological impairment and quality of life after skull base meningioma resection: size and location matter. J Neurosurg. 2017 Dec;127(6):1467-1468.

D. Additional Information: Research Support

Prior Research Grants / Awards:

1. Principal Investigator, NIH Loan Repayment Award Renewal (2016 - 2017) $35,000/yr for loans
"Physiologic mechanisms of naming in the anterior temporal lobe" Mentor: Matthew Howard III, MD

2. Principal Investigator, NIH NINDS F32 NRSA Training Grant (2014 - 2016) $59,888/yr
"Electrophysiology of proper naming in the human left anterior temporal lobe"
Mentors: Daniel Tranel, PhD and Matthew Howard III, MD

3. Principal Investigator, NIH Loan Repayment Award (2014 - 2016) $35,000/yr for loans
"Physiologic mechanisms of naming in the anterior temporal lobe" Mentor: Matthew Howard III, MD

4. Principal Investigator, Medical Student Research Training Award (2007) $4,500
"Electrocorticographic analysis of motor speech" Mentor: Jeffrey Ojemann, MD

5. Principal Investigator, Mary Gates Research Grant, University of Washington (2005) $3,000
"Alterations in pial arteriolar reactivity following subarachnoid hemorrhage" Mentor: Gavin W. Britz, MD, MPH

BIOGRAPHICAL SKETCH
NAME: Holt, Lori L.

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin - Madison	B.S.	1995	Psychology
University of Wisconsin - Madison	Ph.D.	1999	Psychology/Neurosci

A. Personal Statement

As a Professor of Psychology at Carnegie Mellon University, I am affiliated with Pittsburgh's Center for the Neural Basis of Cognition and CMU's Neuroscience Institute, and University of Pittsburgh's Center for Neuroscience. For the last 20 years, my laboratory has investigated human auditory cognitive neuroscience, with a focus understanding how humans interpret the complexity of spoken language. This research program has developed theory and evidence demonstrating that human speech recognition can be considered to arise from general, and not uniquely human or speech-specific, mechanisms. The work extends to understanding of learning and attention in perception of complex sounds, generally. My training includes single-unit electrophysiology, animal behavioral models of audition, and computational modeling, in addition to human behavioral methods across development. My current research program capitalizes on human psychophysics and learning paradigms in adults and children and incorporates human electrophysiology (EEG), neuroimaging (fMRI), and acoustic analyses. My research has implications for critical periods in development, for developmental disabilities involving language, for communication disorders, for advancing language learning in adulthood, and for research on computer understanding of speech. The proposed project will leverage my expertise in auditory processing across complex sound, cortical auditory and learning attention, and speech processing.

In the context of the proposed project, my laboratory can lend deep expertise on perceptual weighting strategies in speech processing which has been a focus of our research for more than a decade. The stimuli and behavioral paradigms described in the proposed project were developed in my lab and have been the subject of extensive empirical research, computational modeling, and theoretical development.

Over the course of my career, I have mentored more than 40 undergraduates, 8 Ph.D. students (serving on committees of an additional 10 students), and 5 post-doctoral researchers. As a mentor I encourage trainees to engage with researchers outside the laboratory, to develop a wide arsenal of methods, and to direct their skills to furthering science whether in or outside the academy. I am deeply committed to supporting diversity in science. I have developed and taught undergraduate courses in Research Methods (with hands-on laboratories), the Biological Foundations of Behavior, and Auditory Cognitive Neuroscience. My leadership in graduate education demonstrates my commitment to training and diversity. Since 2007, I have served as co-Director of the *Predoctoral Training Program in Behavioral Brain Research* (T32GM081760, with co-Director Dr. Julie Fiez, University of Pittsburgh), an NIH-supported initiative to train the next generation of behavioral researchers to employ biomedical techniques in their research.

B. Positions and Honors

Positions

Assistant Professor, Carnegie Mellon University, 1999-2004
Associate Professor, Carnegie Mellon University, 2004-2010

Professor, Carnegie Mellon University, 2010-present

Honors

James McKeen Cattell Sabbatical Award, 2015
National Academy of Sciences Troland Award, 2013
Virginia W. Toomey Award in Auditory Science, 2008
Evie and Ron Krancer Award in Auditory Science, 2007
Association for Psychological Science, Rising Star, 2007
American Speech Language and Hearing Association, Dennis Klatt Research Award, 2002
National Academy of Sciences, 14th Annual Beckman Frontiers of Science Symposium, 2002
James S. McDonnell Foundation 21st Century Scientist Award - Bridging Mind, Brain & Behavior, 2000
Acoustical Society of America, Young Investigator Award, 1999

C. Contribution to Science

(1) Speech perception is founded on general cognitive and perceptual mechanisms rather than specialized processes. My theoretical perspective derives from the idea that speech perception developed among speakers already in possession of perceptual and cognitive systems equipped to deal with natural environments. I suggest that rather than developing novel neural mechanisms with which to accommodate sound produced by a human vocal tract, speech perception exploits existing general perceptual and cognitive processes. This leads to the conclusion that the challenge of perception of speech sounds shares much with perception of other complex events. The essence of this approach is to determine to what extent speech employs general processes before postulating specialized mechanisms. This approach is unorthodox in the field of speech perception, for which the dominant theory has long posited a unique set of representations and processes to accommodate speech signals. It departs somewhat, as well, from traditional study of the auditory system. In particular, there has been a tradition in auditory science to work from the bottom-most levels to understand, in great detail, the input and output relationships of the system under highly controlled circumstances. This approach has provided considerable insight, particularly with respect to peripheral processing. However, a by-product has been the implicit treatment of the auditory system as a passive decoder, implying that if we can understand limits of auditory resolution at various levels, we will have understood sound perception. Practically, this has meant that the tradition has been to examine very simple sounds in isolation. From my theoretical perspective, the representation and processing of speech are not fundamentally different from other complex auditory signals. But, neither can speech processing be accounted for by simple psychoacoustic principles. Instead, we must begin to integrate auditory science into a domain better described as auditory cognitive neuroscience, considering the richness of the acoustic (and, in fact, cross-modal) perceptual environment, its regularity and structure, the influences of short- and long-term experience, and the effects of higher-order knowledge and processing.

- Holt, L. L. & Lotto, A. J. (2010). Speech perception as categorization. *Attention, Perception & Psychophysics*, 72, 1218-1227, PMC2921848.
- Diehl, R. L., Lotto, A. J. & Holt, L. L. (2004). Speech perception. *Annual Review of Psychology*, 55, 149-179.
- Holt, L. L. & Lotto, A. J. (2008). Speech perception within an auditory cognitive science framework. *Current Directions in Psychological Science*, 17, 42-46. PMC2593873.
- Lotto, A. J., & Holt, L. L. (2015). Speech perception: The view from the auditory system. Invited contribution to appear in G. Hickok and S. Small (Eds). *The Neurobiology of Language.*

(2) Understanding auditory categorization. Categorization of complex signals is a central problem for cognitive science; speech categories, with their inherent complexity and multidimensionality, provide an exemplary opportunity to investigate categorization. Speech categories are defined by multiple acoustic cues, none of which is typically necessary or sufficient for marking category membership. Moreover, these cues are usually not perceptually equivalent; some acoustic dimensions are more perceptually significant, or more heavily perceptually weighted, than others. Moreover, both the set of cues signaling the category and the perceptual weighting of these cues is native-language-dependent. Surprisingly (given the vast literature on visual categorization), we know little about auditory categorization to guide understand speech categorization. My work is filling this gap with development of novel methods, empirical behavioral research in speech and nonspeech auditory category learning, examination of impaired populations, and neuroimaging. This is important because

many disorders of communication are characterized by poor speech categorization. Understanding the learning mechanisms that underlie auditory category learning contributes more refined models of speech communication, and has transparent clinical implications.

- Gabay, Y., Dick, F., Zevin, J. D., & Holt, L. L. (2015). Incidental auditory category learning. *Journal of Experimental Psychology: Human Perception & Performance,* 41, 1124-1138. PMC4516559.
- Lim, S, -J., Lacerda, F., & Holt, L. L. (2015). Discovering functional units in continuous speech. *Journal of Experimental Psychology: Human Perception & Performance,* 41, 1139-1152. PMC4601578.
- Lim, S. –J. & Holt, L. L. (2011). Learning foreign sounds in an alien world: video game training improves non-native speech categorization. *Cognitive Science,* 35, 1390-1405. PMC3166392.
- Leech, R., Holt, L. L., Devlin, J. T., Dick, F. (2009). Expertise with artificial non-speech sounds recruits speech-sensitive cortical regions. *Journal of Neuroscience, 29,* 5234 –5239. PMC2747609.

(3) Context dependence in auditory processing. Complex sounds like speech are not perceived simply as a sum total of their frequency and loudness limens. Moreover, sounds presented in sequence interact in perceptual processing, so understanding the representation of each in isolation does little to describe how they are perceived in context. In my view, perceptual systems seek out structure in the world and respond to changes in the environment. As a consequence, context must be considered a critical component in perceptual processing. The “interference” introduced by context is not disruptive of perceptual processing, but fundamental to its adaptive operation in developing and constraining a percept from information that lasts for mere moments. I have contributed to understanding the multiple levels at which auditory processing rapidly tunes to incoming information, and applied these insights to central phenomena of speech perception, such as compensation for coarticulation and talker normalization.

- Holt, L. L. (2005). Temporally non-adjacent non-linguistic sounds affect speech categorization. *Psychological Science, 16,* 305-312.
- Huang, J. & Holt, L. L. (2009). General perceptual contributions to lexical tone normalization. *Journal of the Acoustical Society of America,* 125, 3983-3994. PMC2806435.
- Holt, L. L. (2006). The mean matters: Effects of statistically-defined non-speech spectral distributions on speech categorization. *Journal of the Acoustical Society of America*, *120*, 2801-2817. PMC1635014.
- Laing, E. J. C., Liu, R., Lotto, A. J., & Holt, L. L. (2012). Tuned with a tune: talker normalization via general auditory processes. *Frontiers in Psychology*, 3, 203. PMC3381219.

(4) Dissociable computational principles of subcortical regions contribute to speech learning. Contemporary behavioral research makes clear that learning is a fundamental aspect of speech comprehension. Listeners learn to map highly variable acoustic speech sounds to representations that capture long-term regularities of the language community, such as the inventory of native-language speech sounds (phonemes) and words. But, they also maintain enough flexibility to adapt when speech deviates from community norms, like foreign-accented or noise-distorted speech. Although research increasingly emphasizes the dynamic, flexible nature of speech perception, core theoretical issues remain unresolved. Neurobiological models of spoken language have been largely focused on relatively stable aspects of cerebral cortical processing, and theoretical models detailing dynamic aspects of speech learning have employed learning mechanisms that are incompatible with biological or behavioral data. My recent research is contributing to next-generation neurobiological models that fully incorporate the dynamic, adaptive nature of speech perception.

- Lim, S.-J., Fiez, J. & Holt, L. L. (2019). Role of the striatum in incidental learning of sound categories. *Proceedings of the National Academy of Sciences, https://doi.org/10.1073/pnas.1811992116.*
- Guediche, S., Holt, L. L., Laurent, P., Lim, S. J., & Fiez, J. (2015). Evidence for cerebellar contributions to adaptive plasticity in speech perception. *Cerebral Cortex,* 27, 1867-1877. PMC4481605.
- Lim, S.-J., Fiez, J. & Holt, L. L. (2014). How may the basal ganglia contribute to auditory categorization and speech perception? *Frontiers in Neuroscience*, 8, 230. PMC4117994.
- Guediche, S., Blumstein, S., Fiez, J. A. & Holt, L. L. (2014). Speech perception under adverse conditions: Insights from behavioral, computational, and neuroscience research. *Frontiers in Systems Neuroscience*, 7, 126. PMC3879477.

(5) The mapping from acoustic input to auditory categories is dynamically adjusted. The dual nature of categorization is quite apparent in speech categorization. Efficient categorization systems must come to stably represent long-term environmental regularities in order to generalize effectively to new information. Yet, they must also maintain enough flexibility to adapt to short-term deviations from the norm. Balance is essential as it would be disadvantageous to be either entirely plastic or entirely inflexible. How this crucial balance is achieved in perceptual categorization is not well understood. In general, little attention has been directed to understanding how established category representations interact with local environmental regularities to influence online categorization, in any domain or modality. The dual nature of categorization presents itself clearly in speech. In recent work, I have made contributions to understanding the establishment of long-term perceptual weights for phonetic categories and to understanding how listeners dynamically adjust these weights in response to short-term input that deviates from long-term norms.

- Zhang, X. & Holt, L. L. (2018). Simultaneous tracking of co-evolving distributional regularities in speech. *Journal of Experimental Psychology: Human Perception & Performance*, 44, 1760-1779.
- Idemaru, K. & Holt, L. L. (2013). The long developmental trajectory of children's perception and production of English /r/-/l/. *Journal of the Acoustical Society of America,* 133, 4232-4246. PMC3689790.
- Idemaru, K. Holt, L. L., & Seltman, H. (2012). Individual differences in cue weights are stable across time: the case of Japanese stop lengths. *Journal of the Acoustical Society of America,* 132, 3950-3964. PMC3528741.
- Idemaru, K. & Holt, L. L. (2011). Word recognition reflects dimension-based statistical learning. *Journal of Experimental Psychology: Human Perception & Performance,* 37, 1939-1956. PMC3285244.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/lori.holt.1/bibliography/41159142/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

T32GM081760 (Fiez/Holt) 07/01/2007-06/30/2022
National Institutes of Health (NIGMS) 0.5 Calendar
Predoctoral Training Program in Behavioral Brain Research (Institutional T32) $1,485,792
The overall goal of this training program is to train the next generation of behavioral science researchers who can skillfully incorporate neuroscience perspectives and methods into their programs of research, based on an understanding of brain structure and function that bridges across traditional areas of behavioral research.
Overlap: None

BCS_xxx (Holt/Dick)
National Science Foundation 03/01/2020-02/28/2024
Incidental learning across statistically-structured input in active tasks.
Recommended for funding/pending
This project investigates how listeners acquire auditory and speech categories incidentally in the course of performing other tasks.
Overlap: None

BCS_xxx (Holt)
National Science Foundation 03/01/2020-02/28/2024
Doctoral Dissertation Research: Mechanisms of adaptive plasticity in speech perception $10,800
Recommended for funding/pending
This project supports dissertation research related to dimension-based statistical learning carried out by Charles Yunan Wu.
Overlap: None

R01DC017734 (Holt)
National Institutes of Health (NIDCD) 01/01/2020-12/31/2025

Dimension-based auditory selective attention $2,334,776
This project investigates human listeners ability to direct attention to specific frequency bands in complex sounds.
Overlap: None

R13DC018243 (Holt)
National Institutes of Health (NIDCD) 01/01/2020-12/31/2022
Symposium on Cognitive Auditory Neuroscience $74,131
This grant supports a conference on cognitive auditory neuroscience, to be hosted in Pittsburgh in 2020 and 2022.
Overlap: None

Binational Science Foundation (Holt) 05/01/2016-04/30/2019
0.25 Calendar
$151,200
The dynamics of procedural auditory category learning in developmental dyslexia
The main project goal is examination of online learning, consolidation and retention in children with developmental dyslexia and matched controls
Overlap: None

BCS1655126 (Holt) 04/15/2017-03/31/2021
National Science Foundation 2.0 Calendar
$974,755
Trajectories of acquisition and consolidation in incidental auditory category learning
The main project goal is examination of the developmental course of incidental auditory category learning in typical children and those with dyslexia
Overlap: None

4500002827 09/01/2018-08/31/2020
Department of Defense (Tager-Flusberg) 0.25 Calendar
$79,986
A novel intervention for training auditory attention in adolescents with autism spectrum disorder (ASD).
The main project goal is development of software to support auditory attention training in ASD.
Overlap: None

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ❍ Yes ❍ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

❍ Yes ❍ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

❍ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

Tracking Number: GRANT13169283 Funding Opportunity Number: PA-20-196 . Received Date: 2020-07-15T15:11:48.000-04:00

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ○ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ● No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

6. Change of Investigator/Change of Institution Section

☐ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

☐ Change of Grantee Institution

*Name of former institution:

PHS 398 Modular Budget

OMB Number: 0925-0001
Expiration Date: 02/28/2023

Budget Period: 1

Start Date: 04/01/2021 End Date: 03/31/2022

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
	[redacted]
	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	[redacted]	[redacted]	[redacted]	[redacted]
2.				
3.				
4.				

Cognizant Agency
(Agency Name, POC Name and Phone Number)
U.S. Department of Health and Human Services Steven Zuraf 301-492-4855

Indirect (F&A) Rate Agreement Date 05/13/2020

Total Indirect (F&A) Costs [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($) [redacted]

Tracking Number: GRANT13169283
Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

PHS 398 Modular Budget

Budget Period: 2

Start Date: 04/01/2022 End Date: 03/31/2023

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	[redacted]
	[redacted]
	[redacted]

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	[redacted]	[redacted]	[redacted]	[redacted]
2.	[redacted]	[redacted]	[redacted]	[redacted]
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): U.S. Department of Health and Human Services Steven Zuraf 301-492-4855

Indirect (F&A) Rate Agreement Date: 05/13/2020

Total Indirect (F&A) Costs: [redacted]

C. Total Direct and Indirect (F&A) Costs (A + B) Funds Requested ($): [redacted]

Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium Indirect (F&A) for Entire Project Period ($) [redacted]

[redacted]

2. Budget Justifications

Personnel Justification [redacted]Personnel_Justification.pdf

Consortium Justification NIH_R21_CMU_Budget_Justification.pdf

Additional Narrative Justification

Tracking Number: GRANT13169283 Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

BUDGET JUSTIFICATION

[redacted]

SENIOR / KEY PERSONNEL

Multiple Principal Investigator, Taylor J. Abel, MD, 5% Effort / 0.60 Calendar Months
Dr. Abel is an Assistant Professor and Surgical Director of the Pediatric Epilepsy Surgery Program at [redacted] Medical Center (UPMC) Children's Hospital of Pittsburgh. His clinical expertise is in pediatric neurosurgery, with a focus on epilepsy surgery and steroelectroencephalograpy (sEEG). Dr. Abel's primary research interest is understanding how human auditory cortex mediates voice and speech perception. For this project, Dr. Abel will oversee all sEEG research activities, including project development, simultaneous EEG and sEEG data acquisition, processing, analyses, interpretation, and dissemination of results via presentations and manuscripts. He will also supervise postdoctoral researchers and project personnel at UPMC Children's Hospital of Pittsburgh.

OTHER PERSONNEL

Postdoctoral Fellow, TBA, 100% Effort / 12 Calendar Months
A postdoctoral research associate with training in sEEG and EEG methods will be hired to support the PI and the research team on implementation of planned research activities at UPMC Children's Hospital of Pittsburgh. Specifically, the postdoctoral research associate will be responsible for supporting data acquisition, processing, and analyses of sEEG and EEG data. Additional responsibilities will include assisting with participant recruitment, ensuring ethical and consistent implementation of research activities, and dissemination of study findings.

Research Coordinator, TBA, 50% Effort / 6.00 Calendar Months
A Bachelor's level research coordinator will be hired to oversee administrative management of the project at UPMC Children's Hospital of Pittsburgh. The research coordinator will oversee recruitment of patients, IRB management, including ensuring adherence to IRB regulations for all research procedures, and ensuring compliance will all research regulations at UPMC Children's Hospital of Pittsburgh.

SUPPLIES

Funds are requested for supplies both year 1 and year 2, with lower supply costs in year 2 anticipated with completion of patient-subject enrollment before the end of the year.

BUDGET JUSTIFICIATION
CARNEGIE MELLON UNIVERSITY

SENIOR / KEY PERSONNEL

Principal Investigator, Lori L. Holt, Ph.D.

Dr. Lori Holt is a Professor of Psychology at Carnegie Mellon University with an appointment in the university's Neuroscience Institute and the Department of Modern Languages, a courtesy faculty appointment at the [redacted] Department of Neurosciences and Center for Neuroscience, [redacted] graduate training program. Her expertise is in human auditory cognitive neuroscience, with emphasis on speech communication. Along with Dr. Abel, Dr. Holt will be responsible for managing all aspects of the project, including crafting and executing the experiments, supervising the junior researchers and staff, managing data, and dissemination of results. She will work closely with Dr. Abel to supervise all aspects of the project, including scientific and management oversight and manuscript preparation. Dr. Holt will be the contact PI for grant reporting. The CMU fringe benefit rate is 24.5%, 5% Effort.

OTHER PERSONNEL

Graduate Student, TBA

Partial stipend support (29%) is requested to support the involvement of a graduate student pursuing the PhD in the research. The student will meet one-on-one with Drs. Holt and Abel to discuss project goals, with additional meetings as necessary to support her/his training. The student will work closely with the postdoctoral scholar toward project aims. The student will be recruited through the CMU Department of Psychology PhD, the Cognitive Neuroscience PhD, or the Program in Neural Computation PhD graduate programs. 100% appointment with stipend, tuition and fees, 24.5% fringe benefits.

Indirect Costs

Overhead on this proposal has been calculated at our current proposed or negotiated rate for all fiscal years in accordance with OMB Circular A-21, Section G.7.The modified total direct cost base (MTDC) amount used in calculating the indirect costs is the total direct costs, excluding capital equipment (items over $5,000 per unit), graduate student tuition remission, and individual subcontract costs in excess of $25,000.

Overhead Rate: 55.4%

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 02/28/2023

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	2020_NIH_R21_PerceptualWeights_Introduction_fi.pdf
Research Plan Section	
2. Specific Aims	2020_NIH_R21_PerceptualWeights_SpecificAims_fi.pdf
3. Research Strategy*	2020_NIH_R21_PerceptualWeights_ResearchStrateg.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	2020_NIH_R21_MultiPIPLAN_final.pdf
8. Consortium/Contractual Arrangements	
9. Letters of Support	
10. Resource Sharing Plan(s)	2020_NIH_R21_PerceptualWeights_DataSharing_fin.pdf
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Tracking Number: GRANT13169283
Funding Opportunity Number: PA-20-196. Received Date: 2020-07-15T15:11:48.000-04:00

INTRODUCTION TO THE RESUBMISSION. We wish to thank the panelists for their thoughtful reviews and the constructive criticism that has led us to thoroughly revise the proposal. We are very pleased the panel found our proposal to be *"excellent"* with the "*potential for high impact*." Panelists collectively appreciated the strength of the design, the strong behavioral support for the hypotheses, and the targeted tasks. They found combined stereoelectroencephalography (sEEG) and scalp electroencephalography (EEG) to be an innovation that will build a bridge to non-invasive human studies. These project elements remain at the center of the revised proposal. Reviewers expressed some concern about project feasibility. With sincere appreciation for the detailed communication of this concern to us, we have revised the application in the following ways:

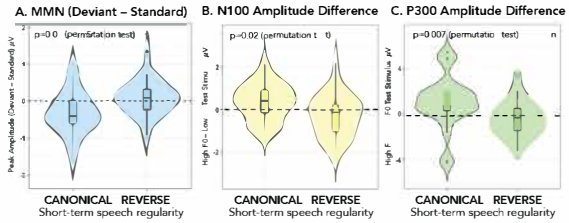

Figure A, Pilot EEG. Difference in event-related potentials for two stimuli varying in F0 as a function of short-term speech regularities (Canonical, Reverse). Differences in MMN **(A)**, N100 amplitude **(B)**, and P300 amplitude **(C)**, are apparent in Canonical, but not Reverse blocks. N=23, mean 20 yrs old.

(1) New EEG pilot data demonstrate feasibility. We have collected new scalp EEG data from teenagers and young adults using the Aim 2 stimuli/task. Behavioral results demonstrate that the diagnosticity of acoustic dimensions like fundamental frequency (F0) in speech categorization is modulated by statistical regularities across short-term speech input (e.g., foreign accent, Reverse block, **Figure 2**). **Figure A** shows that there is corresponding modulation of cortical auditory-stimulus-evoked responses to voice onset time (VOT)-ambiguous Test stimuli differentiated only by fundamental frequency (F0; blue/green symbols, **Figure 2a**) across three EEG measures: mismatch negativity (MMN, passive listening), N100 amplitude (overt categorization), and P300 amplitude (overt categorization). Test stimuli varying in F0 were less well-differentiated in neural response in the context of a short-term regularity with an 'accent' (Reverse), compared to when short-term regularities mirrored English (Canonical), a result consistent with behavioral down-weighting of F0 in the Reverse block (**Figure 2b**). Thus, scalp EEG with relatively low SNR (relative to sEEG) is sensitive to dynamic change in perceptual weights across evoked potentials widely held to originate from distinct cortical generators.[53-55] These pilot results underscore project feasibility and suggest that the greater sensitivity and localization afforded by intracerebral sEEG will important yield important insights in how speech is flexibly represented across the supratemporal plane (STP).

(2) Stimulus specificity. By design, we test our seven hypotheses across a simple, but powerful, behavioral model backed by extensive prior research.[24-29] Our prior and ongoing behavioral and EEG research demonstrates that these effects scale to other speech contrasts, continuous speech, and to passive listening. Thus, the approach balances careful control with evidence for future scalability. This 'sweet spot' is chosen intentionally to deliver foundational data with the potential to deeply inform future research.

(3) New sEEG pilot data demonstrate sensitivity to F0 and VOT acoustic dimensions, supporting project feasibility. This particular stimulus testbed also pairs particularly well with sEEG. In new sEEG pilot data (**Figure 3**) we demonstrate that 7 of 7 patients exhibited at least one STP channel with significant graded variation in high-gamma activity to both VOT and F0 dimensions. We note that this is likely to be a conservative estimate as these pilot data were collected during passive listening to continuous speech: pre-lexical representations tend to be amplified in overt speech categorization tasks like those proposed here. Finally, we note that prior research demonstrates graded scalp-recorded N100 responses to stimuli varying across VOT[56,57] and F0.[58,59]

(4) Cortical Sampling with sEEG. Reviewers expressed concern about sparse cortical sampling with sEEG, but electrodes will be situated in stereotyped, constrained positions that always include an individual's planum polare, Heschl's gyrus, and planum temporale along the STP. This provides a consistent assay of anatomo-functional regions across subjects that, as evident in new sEEG pilot data (**Figure 3**), exhibit sensitivity to F0 and VOT dimensions. This presents an ideal testbed for our seven hypotheses, especially leveraging the power of within-subject/within-electrode responses to the same speech stimuli presented across distinct experimental contexts that have been shown to influence perceptual weights. It is important to note that the project also will yield rich data from sEEG electrodes placed across cortex in the same subjects (**Figure 4**) that, while not the specific focus of this 2-year-long R21 project, will support rich secondary hypotheses sure to inform future work.

(5) Under-specification. Aspects of our approach were underspecified in the original proposal. Here, we provide much more detail about *Inclusion/Exclusion Criteria* (see **Human Subjects**) and *Patients Meeting Criteria Over the Last 2 Years* (see **Human Subjects, Table I**), *Statistical Analysis* (see **Statistical Design** and **Approach**), *Clinician/Scientist Conflict of Interest* (see **Data Safety and Monitoring Plan**), *Age Range* (see **Approach, Human Subjects, Inclusion of Women, Minorities and Children**), *Clinical Rationale for STP Electrodes* (**Human Subjects**), and *Power* (**Approach**) that attest to the feasibility of the proposed research.

SPECIFIC AIMS. Understanding spoken language is predicated on clarifying how the detailed features of speech influence neural representation. In recent years, intracranial electrophysiology has supported rapid advancement in understanding human cortical speech processing to reveal that fundamental acoustic-phonetic dimensions are represented in neural response across superior temporal gyrus (STG). This moves us forward in 'cracking the speech code.' Yet, contemporary behavioral research demonstrates that acoustic-phonetic speech dimensions do not stably map to phonemes. Instead, the multiple acoustic dimensions that signal phonemes carry different *perceptual weights* that rapidly and flexibly shift according to listening demands and context. The very input dimensions that inform speech recognition are flexible, not fixed, and we do not yet know how this relates to cortical response. Filling this gap is especially crucial since nonnative speakers of English outnumber native speakers 3 to 1 worldwide. Thus, flexible mapping across the systematic variability of accents and dialects is the norm – not an exception – and is an important factor in communication disorders. Our scientific premise is that next-generation neurobiological models must account for *adaptive plasticity* – the dynamic, flexible mapping of speech acoustics to perception.

Our central objective is to break new ground in understanding how human cortical response to speech represents perceptual weights of acoustic dimensions signaling phonemes, and how the neural code changes as perceptual weights flexibly adjust under different listening demands. We take a unique approach that marries classic and cutting-edge methods and the complementary strengths of a collaborative research team. Using intracerebral recordings via stereoelectroencephalography (sEEG) obtained in neurosurgical procedures, we will assess neural representation not just across STG but also (owing to the depth of sEEG electrodes) through the supratemporal plane (STP) that includes superior temporal sulcus (STS) and Heschl's gyrus (HG). Additionally, we will acquire simultaneous scalp electroencephalography (EEG) allowing us to link intracerebral recording with long-standing approaches appropriate for healthy listeners. Using a well-studied suite of behavioral paradigms, we will precisely manipulate acoustic dimensions, and the short-term speech regularities in which they are experienced, to influence the diagnosticity, or *perceptual weight*, of acoustic-phonetic dimensions in signaling phonemes.

Aim 1 will establish whether neural responses across the supratemporal plane (STP) reflect the perceptual weight of acoustic dimensions. Although multiple acoustic dimensions contribute to speech recognition, they do not contribute equally. Some carry more perceptual weight than others and these baseline perceptual weights appear to be established by long-term experience with speech input distributional regularities. Prior studies demonstrate the neural validity of acoustic-phonetic dimensions across the STG, but have not addressed changes in representation as a function of perceptual weight. We predict that response across the STP will be modulated as a function of the perceptual weight of a dimension in signaling a particular phoneme. Aim 1 tests this by examining the neural representation of two acoustic-phonetic dimensions as a function of their behaviorally-assessed perceptual weight across the STP, including superior temporal sulcus (STS) and Heschl's gyrus (HG). Examining behavior, sEEG, and scalp EEG simultaneously will leverage the sensitivity and localization afforded by intracerebral sEEG to better understand neural representation of perceptual weights in speech categorization, while also building doing crucial groundwork to link back to noninvasive approaches suitable outside a neurosurgical context.

Aim 2 will test whether neural responses in the supratemporal plane flexibly adjust. Changes in context, background noise, and even statistical regularities of speech across time (e.g., a foreign accent) influence the perceptual weights of acoustic dimensions, demonstrating the dynamic nature of the mapping of input to speech representations. Aim 2 will examine behavioral speech categorization, sEEG, and scalp EEG in the participants for whom baseline perceptual weights are measured in Aim 1. Our approach will be to use two well-established behavioral manipulations that lead to shifts in perceptual weights relative to baseline: introduction of noise and introduction of an 'accent' for which the short-term speech input deviates from distributional regularities of the native language. We predict these manipulations will shift neural responses relative to those observed at baseline in Aim 1 in a manner directionally predictable according to shifts in behavioral perceptual weights. Here, as in Aim 1, simultaneous scalp EEG will complement sEEG to connect invasive methods in clinical populations and noninvasive measures available in studying healthy listeners.

Across aims, our pilot behavioral, EEG, and sEEG data support project feasibility. This Exploratory/Developmental R21 project will be to establish a means by which to fill a crucial gap in understanding speech representation in human cortex, with the possibility of radically shifting existing conceptual models and substantially advancing current understanding. As well, the research will build a bridge between invasive and noninvasive human electrophysiology. Further, it will establish a new research team with complementary strengths spanning neurosurgery, speech perception, and auditory cognitive neuroscience.

SIGNIFICANCE. A simple utterance like *beach* is distinguished from its near-neighbor *peach* by as many as 16 acoustic input dimensions.[1] The details of how these dimensions are expressed varies as a function of whether *beach* is part of a story told by John or Mary, whether the talker speaks British or American English, and even whether the storytelling venue is quiet or noisy. Research directed at understanding speech comprehension has long grappled with how complex acoustic input relates to native-language representations for phonemes, the linguistically distinct units of sound that differentiate meaning like the [b] and [p] in *beach* versus *peach*. Intracranial neurosurgical techniques have rapidly advanced understanding of human cortical response to speech. There is now robust evidence that superior temporal gyrus (STG) plays a crucial role in extracting meaningful linguistic features from speech input, with consonant and vowel acoustic-phonetic dimensions apparent in the tuning of neural populations.[2,3] This success can give the impression, at least implicitly, of a stable mapping from acoustic input dimensions to native-language speech representations, much like had been the starting point of traditional theoretical accounts.[4] However, a rich behavioral research literature now demonstrates that the mapping of acoustic input dimensions to speech representations varies substantially across listeners and is malleable according to listening context. This *adaptive plasticity* – the dynamic, flexible mapping of speech acoustics to perception – is not yet well integrated into models of cortical speech processing. This proposed Exploratory/Developmental R21 project will lay the groundwork for developing new neurobiological models that accommodate the following well-established characteristics of speech processing:

(1) Acoustic dimensions do not signal phonemes with equal 'perceptual weight'. Although the simple distinction between *beach* and *peach* can involve covariation among as many as 16 acoustic dimensions, these dimensions to not contribute equally. Some more robustly signal speech category identity than others: they carry more *perceptual weight*.[5–11] For example, among the dimensions signaling *beach* vs. *peach,* voice onset time (VOT, the time between consonant release and the onset of voicing in the vowel) tends to carry greater perceptual weight in the sense that it is more strongly associated with category identity than fundamental frequency (F0, the frequency of voicing in the vowel), which also covaries with [b] vs. [p] and somewhat less strongly signals category identity. This is apparent when speech acoustics are parametrically manipulated across VOT and F0 to vary perceptually between *beach* and *peach* and the contribution of each dimension to categorization responses is estimated using regression models. On average, listeners rely predominantly upon VOT in quiet, with F0 signaling category membership to a lesser extent (**Figure 1a,b**). Our understanding of cortical response to speech does not yet reflect *perceptual weight,* the relative strength of the influence of sensory input on speech categorization.

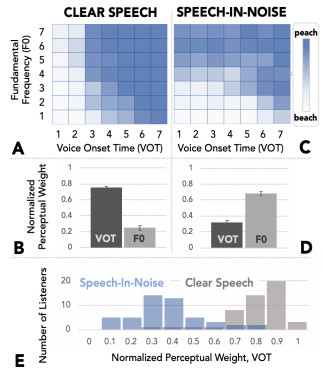

Figure 1. Pilot Data. Clear Speech (left) and Speech-in-Noise (right) varying acoustically across F0 and VOT and perceptually from *beach* (white) to *peach* (blue). **(A, C)**, Categorization over orthogonal acoustic dimensions provides data from which to calculate baseline perceptual weights, shown as relative perceptual weights in **(B, D)**. Listening context (clear, speech-in-noise) causes the same listeners to rely upon different acoustic dimensions to categorize speech; VOT is dominant in clear speech whereas F0 is dominant in noise. **(E)**, These same teenage and young-adult subjects (mean 20yrs) exhibit substantial heterogeneity in weights in each context.

(2) Individuals exhibit stable perceptual weights within a listening context, but weights shift substantially across contexts. Whereas VOT carries greater perceptual weight for *beach* vs. *peach* in quiet, F0 more effectively signals category identity in modest noise (**Figure 1c,d**).[12] *Perceptual weights are labile; perception relies on different input dimensions in different listening contexts*. As a result, understanding the representation of VOT (or any acoustic dimension) in a single context takes us only part of the way to understanding how the auditory system maps the complex acoustics of speech to meet the communicative demands of everyday listening. A better understanding of the dynamic, flexible nature of speech processing will advance understanding of communication in listening conditions that are typical of natural environments and will be especially important for understanding listeners with hearing loss and communication disorders, for whom perceptual weights often differ from healthy listeners at baseline.[13]

(3) Individuals differ in baseline perceptual weights. An added complication is that individuals differ in baseline perceptual weights (**Figure 1e**). These differences are stable across time suggesting that they reflect underlying processing rather than measurement fluctuation.[14] For example, even among listeners who consistently weight VOT more than F0 there is considerable individual variation in the extent to which individuals rely upon F0 in signaling contrasts like *beach* vs. *peach*.[15–19] Thus, careful examination of variation in baseline perceptual weights can inform understanding of cortical response to speech, especially in samples with a good degree of heterogeneity in perceptual weights, like those shown in **Figure 1e**.

(4) Teenagers and young adults exhibit heterogeneity in baseline perceptual weights. Phonetic category development continues well into later adolescence[20,21] such that perceptual weights across acoustic dimensions are not yet fully adult-

like.[14,20] In this regard, examination of speech processing among adolescents offers an opportunity to observe informative perceptual weight heterogeneity (as in **Figure 1e**, mean 20 yrs). The proposed research targets 15- to 25-year-old listeners to capitalize on this heterogeneity, with the premise that graded differences in perceptual weight will relate to graded differences in neural representation. In the proposed project, the richness of this testing ground is amplified by pairing natural heterogeneity in baseline perceptual weights (Aim 1) with experimental manipulation of context in the same listeners to evoke dynamic adjustments to perceptual weight (Aim 2, **Figure 1b,d**) to examine the impact on neural response.

(5) Short-term input regularities also affect perceptual weights. We regularly encounter 'non-standard' pronunciations. A talker may have a strong accent, or a stuffy nose. Although comprehension initially suffers when speech departs from the norms of a listener's language-community, the perceptual system rapidly adapts and comprehension improves. The mapping from acoustics to linguistic representations flexibly accommodates foreign accents[22], signal distortions[23], and audio-visual mismatch[24]. This adaptive plasticity appears to happen at a pre-lexical level of processing.[23] In a broad sense, the very acoustic dimensions that signal speech representations are dynamically, and rapidly, adjusted in online speech processing to accommodate regularities in the ambient speech environment. The mapping of acoustic dimensions to speech representations appears not to be rigidly fixed by long-term experience. Rather, the 'feature space' serving speech recognition adapts to listening context. These effects showcase the need for more dynamic, flexible neurobiological models of the mapping from acoustics to cortical response.

Our scientific premise is that next-generation models of human cortical speech processing must account for adaptive plasticity -- the dynamic, flexible mapping of speech input to perception.

Dimension-based statistical learning (DBSL) is an example of adaptive plasticity in speech perception with a number of properties attractive for pursuing mechanistic questions regarding how the perceptual weight of acoustic dimensions is reflected in cortical response.[25–29] For example, when participants respond to stimuli that vary orthogonally across VOT and F0 dimensions signaling *beach* vs. *peach,* it is possible to measure the relative effectiveness of each dimension in signaling phoneme category responses (**Figure 1a**). In these judgments, it is evident that VOT carries a stronger perceptual weight in quiet and that VOT and F0 exhibit a correlation in their pattern of influence (higher F0s and longer VOTs are each associated with *peach*, upper right quadrant **Figure 1a**). As noted above, these baseline perceptual weights shift upon the introduction of noise (**Figure 1c,d**) and there are stable individual differences underneath these group averages (**Figure 1e**).

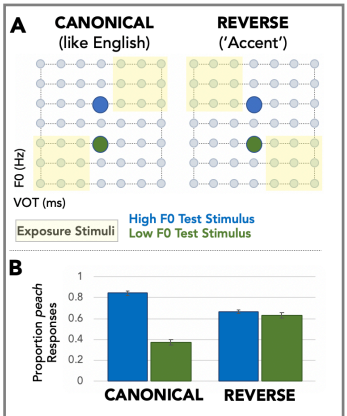

Figure 2. Dimension-based statistical learning (DBSL) Pilot Data. (A) Stimuli are sampled selectively from the VOTxF0 acoustic space (yellow shading) to align with English (Canonical) or to introduce a short-term 'accent' (Reverse). Test stimuli (blue/green) hold VOT ambiguous and vary in F0, measuring reliance on F0 in categorization responses. **(B)** F0 signals category identity in Canonical block. But, in Reverse block it is down-weighted in its utility and does not support differential categorization.

The DBSL paradigm selectively samples stimuli to manipulate short-term speech regularities. Instead of sampling equiprobably across the full 2-d VOTxF0 acoustic space to estimate baseline perceptual weights (**Figure 1a**), stimulus sampling is selective. Across *Exposure* trials (**Figure 2a**, light yellow) this short-term regularity can match the typical VOTxF0 correlation in English (Canonical Block, with higher F0s and longer VOTs for *peach*) or introduce an 'accent' with a short-term VOTxF0 correlation that is opposite that typically experienced in English (Reverse Block, lower F0s with longer VOTs for *peach*). This artificial accent is subtle and introduced unbeknownst to listeners. Yet, it rapidly produces a marked shift in the perceptual weight of F0 in *beach-peach* categorization decisions. This is evident in listeners' responses to *Test* stimuli (blue, green larger symbols in **Figure 2a**) that occur infrequently and are randomly intermixed with *Exposure* stimuli. *Test* stimuli have a neutral, perceptually ambiguous VOT thereby removing this dominant dimension (**Figure 1b**) from adjudicating a category identity decision. But, F0 varies across the *Test* stimuli. Therefore, the proportions of *Test* stimuli categorized as *beach* vs. *peach* provide a metric of the extent to which F0 is perceptually weighted in categorization as a function of the different short-term speech input regularities experienced across Canonical and Reverse blocks. **Figure 2b** shows that listeners rapidly re-weight F0 reliance upon introduction of the accent (Reverse block). Thus, the effectiveness of acoustic dimensions in signaling speech categories, their *perceptual weight*, dynamically adjusts according to short-term experience across acoustic input dimension regularities.

Flexible speech representation in human cortex. Building from these well-established characteristics of speech processing, we propose to undertake an Exploratory/Developmental R21 project to measure cortical

response using invasive human neurosurgical sEEG techniques and simultaneous noninvasive scalp EEG to establish *baseline perceptual weights* across orthogonally varying VOT and F0 input dimensions *in quiet* (for which VOT is expected to be dominant; **Figure 1a,b**), *in noise* (for which F0 is predicted to be dominant; **Figure 1c,d**) and also in Canonical and Reverse blocks that *manipulate the short-term input regularities* that have been shown to modulate perceptual weight (**Figure 2b**).

INNOVATION. We take a dynamic approach to speech processing that is not yet well-represented in human cortical models. Although there have been major innovations and advances in understanding the neurobiological bases of human speech perception since the advent of intracranial electrophysiology in human listeners[2,3,32–35], this foundational work has tended to take a relatively static perspective regarding the mapping from speech input to cortical representations (see [32,36] for notable exceptions). However, as emphasized above, these mappings are highly task-dependent and dynamically molded by listening demands. The proposed research is innovative in directly examining dynamic aspects of speech processing under two contexts: in the adverse listening conditions of speech-in-noise and in the context of an 'accent' to which listeners must adapt in DBSL, each of which has important implications for communication disorders.

Our use of sEEG provides unprecedented access to the supratemporal plane (STP). Ground-breaking intracranial EEG research has deeply informed speech coding in human cortex. With some notable exceptions[40,41], this work has focused mostly on extra-pial intracranial recordings on the cortical surface, usually across the STG (electrocorticography, ECoG). However, much of auditory cortex hides deep within the STP where important processing related to selective attention[42] and learning[43–45] that may support adaptive plasticity in speech perception cannot be accessed by ECoG grids. The proposed research will marry the advantages of well-characterized adaptive plasticity tasks with neurosurgical intra*cerebral* sEEG recordings along the STP including electrodes that specifically target both sulcal and gyral grey matter including superior temporal sulcus (STS) and Heschl's gyrus (HG). As **Figure 3** illustrates, when electrodes are placed in the STP, they are situated in stereotyped, constrained positions such that their multiple channels span an individual's Heschl's gyrus, planum polare, and planum temporale to provide a consistent assay of anatomo-functional regions of cortex across subjects (see **Data Safety and Monitoring Plan** for details).

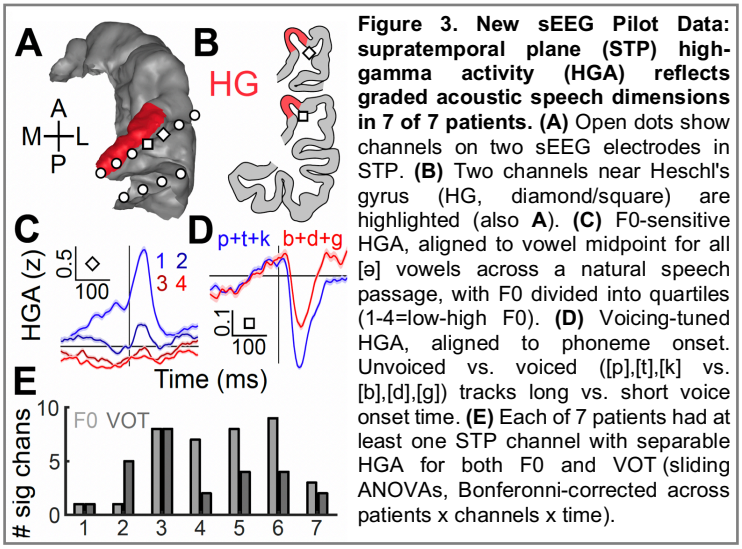

Figure 3. New sEEG Pilot Data: supratemporal plane (STP) high-gamma activity (HGA) reflects graded acoustic speech dimensions in 7 of 7 patients. (A) Open dots show channels on two sEEG electrodes in STP. **(B)** Two channels near Heschl's gyrus (HG, diamond/square) are highlighted (also **A**). **(C)** F0-sensitive HGA, aligned to vowel midpoint for all [ə] vowels across a natural speech passage, with F0 divided into quartiles (1-4=low-high F0). **(D)** Voicing-tuned HGA, aligned to phoneme onset. Unvoiced vs. voiced ([p],[t],[k] vs. [b],[d],[g]) tracks long vs. short voice onset time. **(E)** Each of 7 patients had at least one STP channel with separable HGA for both F0 and VOT (sliding ANOVAs, Bonferonni-corrected across patients x channels x time).

Testing whether speech is flexibly represented in STP addresses crucial theoretical debates. There are central theoretical debates of the nature of top-down versus bottom-up processing schemes, and whether these information sources interact bidirectionally in speech processing (e.g., interactive vs. feedforward[37–39]). Importantly, because we will take an *intracerebral* approach that provides access to early auditory cortical regions like Heschl's gyrus (HG) this study will provide data to inform where in the auditory cortical hierarchy adaptive plasticity effects are apparent. Our pilot sEEG data in **Figure 3** illustrate the feasibility of examination of speech categorization across VOT and F0 acoustic dimensions. High-γ (high-gamma frequency band, ~70-150Hz, a prominent neural signature in intracranial data that has been associated with neuron population level firing rate) activity (HGA) along the STP is graded across stimulus changes in F0 and VOT acoustic dimensions (**Figure 3c,d**). Indeed, each of 7 patients had at least one STP channel with HGA separable according to graded modulations in F0 and VOT (**Figure 3e**). By examining modulation of HGA across experimental contexts we have powerful, and feasible, tests within-subject/within-electrode that will establish the extent to which regions along the STP flexibly represent speech input.

sEEG assists in the 'searchlight' challenge. Inasmuch as human intracranial research must be driven first and foremost by clinical necessity, research faces a 'searchlight' challenge: examination of neural representation where 'the light is shining' by virtue of electrode coverage. In the context of this 2-year project, we direct our hypotheses to the STP because it has high potential for adjudicating theoretically-significant questions. However, it is worth noting that sEEG electrodes cover diverse cortical sites (**Figure 4**), presenting an opportunity to pursue secondary hypotheses. For example, we can investigate whether electrodes in inferior frontal cortex, implicated in the adaptive plasticity of speech processing in adverse listening conditions, exhibit context-sensitive HGA.[60] The broader data set we collect also will establish an informative means by which to test hypotheses across

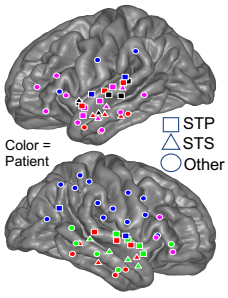

Figure 4. sEEG electrode sites across 5 patients illustrating coverage across the supratemporal plane (STP), superior temporal sulcus (STS) and other brain regions including frontal cortex.

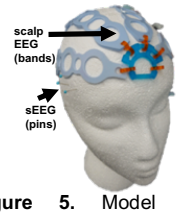

Figure 5. Model of sEEG+EEG approach.

'control' electrode sites, for example even in STP where, in our data, planum polare channels have shown little F0- or VOT-sensitivity.

Combined sEEG+EEG is a major innovation. The placement of sEEG electrodes allows for scalp electrodes to be placed successfully on the central sites most responsive in auditory tasks. This makes it possible to create an enormously informative link across the measurements possible with typical listeners, and listeners undergoing neurosurgery. Pragmatic solutions to combined sEEG+EEG developed in partnership with Carnegie Mellon University aid this innovation (**Figure 5**). With EEG and behavioral alignment with sEEG data, the present project will establish an approach to using EEG as a 'Rosetta Stone' with which, in future larger-scale projects, we aim to be able to affirm – even at the level of individuals – whether patient-participants conform to 'typical' auditory behavior, a vital comparison not yet well-represented in contemporary neurosurgical studies. Feasibility is supported by our new pilot EEG data (**Figure A**).

An adolescent sample supports the research aims, and opens new opportunities. Here, the study of teenagers and young adults is a pragmatic choice not motivated by development *per se*, but instead chosen to capitalize on good heterogeneity in patterns of perceptual weights in this sample, as observed in our pilot data (**Figure 1d, Figure 3**). Nonetheless, we note that from a lifespan perspective adolescence is the great unexplored period of auditory and speech processing despite its importance in many communication disorders. The approaches we develop will support future research directed specifically at developmental questions.

The formation of a new cross-disciplinary research team is a major strength. This project unites unique, and complimentary, strengths of Multiple Principal Investigators (MPIs) that span disciplines at adjacent institutions in Pittsburgh (Taylor Abel, University of Pittsburgh Medical Center (UPMC) Children's Hospital of Pittsburgh (CHP); Lori Holt, Carnegie Mellon University). The project is a natural extension of the MPIs' complementary expertise. All the pieces are in place to assure an integrated project, including frequent in-person meetings and cross-lab mentoring synergies (see **MPI Plan**).

APPROACH. Experiments will be conducted at CHP where MPI Abel is the Surgical Director of the Pediatric Epilepsy Surgery Program. MPI Holt's laboratory is located a short distance from CHP. The requisite patient population, equipment, IRB approval, and local expertise are in place for the proposed work. **Human Subjects** provides a detailed plan for cross-site project management, including a timeline.

Participants and Consent. **Human Subjects** provides full protocol details. In brief, our approach will be to test 25 neurosurgical patients ages 15-25 years, among whom it is possible to measure intracerebral neural response using sEEG with paired scalp EEG. Patient permitting, individuals will complete all tasks across Aims 1 and 2.

Table I. Annual estimates based on 2019 enrollment.

	A	B
L HG	14	14
R HG	12	12
L aSTP	12	12
R aSTP	10	10
L pSTP	14	18
R pSTP	12	16
L aSTS	12	22
R aSTS	10	20
L pSTS	12	12
R pSTS	8	14

Column A: Patients; Column B: Electrodes. (**a**: Anterior; **p**: Posterior; **HG**: Heschl's Gyrus, **STP**: Superior Temporal Plane (relative to HG); **STS**: Superior Temporal Sulcus)

The age range of our sample overlaps with the typical young adults sampled by the larger behavioral literature, and our pilot data indicate desirable baseline heterogeneity in perceptual weights with this sample size and age range (**Figures A, 1, 2, 3**). We expect to enroll an equal male/female patient distribution. *Power and Sample Size*. Robust behavioral effects will allow examination of perceptual weighs in neural representation. Using behavioral effect sizes from **Figure 2** pilot data to estimate the sample size required for a predicted power of 0.8 (two-tailed alpha at .05) yields a sample of N=25. This leaves open the issue of power for neural measures. Our pilot EEG data with the same task/stimuli revealed robust effects with N=23 (**Figure A**), reassuring that N=25 is a reliable target for EEG. The SNR advantages of sEEG versus EEG, and our sEEG pilot data in **Figure 3**, suggest that this sample size will be more than sufficient for sEEG measures, especially as they will be utilized in a within-patient/within-electrode experimental design. *Enrollment*. Based on MPI Abel's neurosurgical enrollment with similar inclusion criteria across 2019 we anticipate no enrollment challenges across this two-year project (see **Table I** and **Recruitment & Retention**). *Inclusion/Exclusion Criteria* are detailed in **Human Subjects**.

Neurosurgical Approach. Electrode implantation is planned based on clinical necessity by epileptologists not involved in the research, protecting against conflict of interest.[46] *No electrode is implanted solely for research purposes*. **Data Safety & Monitoring** provides further details and the clinical rationale for STP electrodes. Post-surgery, patients typically spend a night in the pediatric intensive care unit and then transfer to the epilepsy monitoring unit the following day. Once feeling well (1-2 days postop) patients may consent/assent to participate.

Acoustic Stimuli and Behavioral Approach. The acoustic stimuli have been extensively tested in MPI Holt's research,[25–27,29] with feasibility for our sample attested in pilot data (**Figures A, 1, 2, 3**). Stimuli are derived from natural speech, and subtly manipulated to parametrically vary across the VOT and F0 dimensions. During the post-op period, patients will complete self-paced blocks of trials that simply require listening to a sound diotically over insert earphones and deciding whether the initial consonant is a [b] or a [p]. To facilitate response, we will use minimal pair English words (*beach* vs. *peach,* e.g.) that can be illustrated so that patients can tap a button to indicate which picture matches the word heard. Subjects will categorize stimuli across the 2-d VOTxF0 acoustic grid for clear speech (Aim 1, **Figure 1a**) and speech-in-noise (Aim 2, **Figure 1c**) and across the Canonical-Reverse block structure that introduces an artificial accent in the DBSL paradigm (Aim 2, **Figure 2a**). All manipulations are within-patient, lending considerable power to test our predictions. Crucially, the same *Test* stimuli *are present in each block* (blue/green symbols, **Figure 2a**, also mirrored in **Figure 1a**), providing a 'gold standard' against which to examine how neural response to identical stimuli is modulated as a function of listening contexts that robustly influence perceptual weights in behavioral tasks.

Hypotheses. We hypothesize that (**H1**) broadly, the relative perceptual weight of VOT and F0, as measured behaviorally, will be reflected in cortical response, (**H2**) with modulation as a function of baseline perceptual weights, (**H3**) shifts experimentally invoked by a change in listening context by presenting speech in noise, (**H4**) and by introducing an 'accent' that shifts short-term input regularities across VOT and F0. In the latter case, our approach will allow us to test the specific directional hypothesis (**H5**) that F0 perceptual weights in the DBSL paradigm are both exaggerated by Canonical input regularities that cleanly convey a VOTxF0 correlation consistent with English and that F0 perceptual weights are down-weighted upon introduction of a regularity that violates the typical pattern of English (supported by scalp EEG pilot, **Figure A**). Our use of sEEG allows us to evaluate these hypotheses across the supratemporal plane thereby testing the strong, and falsifiable, hypothesis (**H6**) that adaptive plasticity effects are present in HG versus (**H7**) apparent only at higher levels of the cortical hierarchy. Our ability to test these hypotheses is complemented by sEEG electrode placement in cortical regions outside STP (see **Figure 3**) which will support secondary hypotheses and serve as control electrode sites.

Evaluating the Hypotheses: Behavioral Analyses. We will evaluate the behavioral impact of the VOT and F0 acoustic dimensions on classification using *mixed-effects logistic regression* (with patient as a random effect, stimulus VOT and F0 as fixed effects and classification responses as the outcome). Following our prior work,[14,25–29] perceptual weights for the dimensions will be computed for each patient as the correlation between dimension values and the proportion of *peach* classifications across all stimuli in the VOTxF0 stimulus grid with absolute values of the correlation coefficients normalized to sum to one as an *index of relative perceptual weight* in quiet (Aim 1) and in noise (Aim 2). To examine the impact of a change in 'accent' in the DBSL paradigm, we will use mixed logit models with responses as a function of patient, block, test stimulus F0 and the interaction between block and F0 (Aim 2). Patient will be modeled as a random effect, with the other factors as fixed effects.

Evaluating the Hypotheses: Neural Analyses. We will take a multi-pronged analysis approach. Our pilot data in **Figure 3** demonstrate that *high-γ* activity (HGA) is modulated by graded acoustic details across the VOT and F0 dimensions across electrodes placed in the STP. Following the analysis pipeline used in our pilot data analyses, we will specifically examine stimulus-time-locked HGA to the *Test* stimuli, which possess consistent, perceptually-ambiguous VOT and differentiated F0. We have specific, directional predictions (detailed above) regarding how HGA to F0-differentiated *Test* stimuli will vary according to perceptual weight in behavior. To briefly recap, we expect that HGA to *Test* stimuli will be better differentiated (1) in the Speech-in-Noise compared to the Clear baseline context (because F0 carries greater perceptual weight); (2) in the Canonical, compared to the Reverse, context; (3) in the Canonical, compared to the Baseline Clear Speech context (because stimulus statistics exaggerate the dimension regularity in behavior). We will use *least-squares linear regression neural encoding models* to investigate relationships between acoustic stimulus dimensions and STP neural responses during the baseline quiet context, in which stimuli sample a 2-d F0 x VOT grid. This approach will allow us to identify the subset of electrodes and temporal windows that encode at least one of these 2 dimensions at baseline; targeted analysis on this subset (described below) will then be used to compare listening contexts.

Encoding model inputs will consist of F0 and VOT, with an output of channel- and time-specific HGA. For a given electrode, individual models will be built using single trial data and a sliding window, allowing us to identify the temporal window relative to stimulus onset that yields significant models. Model quality will be assessed in two ways. First, using models built on all trials, we will calculate the regression *F*-statistic, which determines if any coefficients are significant. This will be compared to null distributions estimated with permutation tests that shuffle data across trials. Second, goodness-of-fit will be assessed for significant models by performing leave-one-out cross-validation and calculating R^2, the proportion of variance in neural activity explained by the model. Finally,

we will assess the relative encoding strength of each acoustic dimension using model coefficient *t*-statistics. In summary, this approach will allow us to identify the timing and anatomical location of F0 and VOT encoding during baseline quiet listening conditions for which dimensions are sampled orthogonally (as in **Figure 1a**).

To characterize shifts in neural encoding across listening contexts, we will investigate Noise using encoding models and Canonical/Reverse contexts using *cluster-based approaches*.[32,49] Encoding models will be built from the Noise context for all channels and timepoints, using the same approach as Baseline. If a channel/timepoint is significant in either Baseline or Noise, the F0 and VOT coefficient *t*-statistics will be compared across contexts. We hypothesize that encoding of F0 will strengthen and VOT will weaken in Noise, as measured by changes in *t*-statistic magnitudes across multiple models. Next, we will compare neural responses for each of the two *Test* stimuli (which were embedded in the F0 x VOT grids, **Figure 1a**) between Baseline vs. Canonical and Canonical vs. Reverse. The clustering approach will look only at Baseline significant channels and time windows and involves randomly assigning listening context labels to single-trial data followed by a *t*-test at each time step. Across all permutations, a criterion value will be established for each timepoint (>95% of absolute value of *t*). For each of these permutations, we will next determine whether its value exceeds criterion across timepoints, and for how many timepoints it exceeds criterion (a 'cluster'). For each cluster, *t* values will be summed and assigned to all points in the cluster, with the largest summed cluster value stored for each permutation. This will create a null distribution of 1000 cluster values. We then will establish whether the cluster size calculated across real neural data (organized according to listening context) exceeds the 95% permutation-based cluster values such that $p<.001$ indicates an observed cluster is greater than all permutation-based clusters. Using this approach, we will identify context-dependent shifts in HGA responses, which we predict will reflect observed shifts in perceptual weights. Namely, we hypothesize that HGA responses in F0-encoding channels will be enhanced in the Canonical context relative to both Baseline and the Reverse context. *Rigor and Reproducibility*. Analyses will be controlled for multiple comparisons, with sex as a co-variate in our analyses. We will use pre-registration and provide access to all the deidentified source data.

Potential Pitfalls and Alternative Strategies. *Clinical Sample.* Our goal is the understand normative brain function, but sEEG electrodes are only implanted in patients. We note this strategy has been incredibly informative in prior work. Here, we go further to include scalp EEG as a means of establishing commonalities with healthy listeners, a pursuit still quite rare in intracranial research. *Patient performance*. Presurgical tests will assure basic sensory and language function in patients prior to participation. *Hemisphere.* There is not yet sufficient data to support explicit hemisphere predictions so we will collect data across left and right hemispheres. *Adolescents.* Our participants will include teenagers and young adults (15-25 yrs), as in our behavioral (**Figures 1, 2**), EEG (**Figure A**) and sEEG (Fi**gure 3**) pilot data. This range overlaps substantially with the large literature of speech perception studies examining undergraduate students. We have established (**Figure 1e**) this sample exhibits sufficient heterogeneity in baseline perceptual weights to evaluate perceptual weights as a function of EEG and sEEG (Aim 1), especially in pairing with within-patient/within-electrode experimental manipulations (Aim 2). *Electrode Placement.* Epileptologists not involved in the research determine the clinical necessity of electrode placement, eliminating conflict of interest. When electrodes are placed in the STP (approximately 70% of 2019 caseload), they are situated in stereotyped, constrained anatomic positions that always include an individual's Heschl's gyrus, planum polare, and planum temporale. *Sensitivity to Acoustic Dimensions.* We investigate F0 and VOT acoustic dimensions because our pilot sEEG data (**Figure 3**) demonstrate graded responses across these dimensions in the STP, and in the N100 measured with EEG.[56-59] New EEG pilot data further demonstrate that short-term speech regularities modulate neural response to these dimensions (**Figure A**). This gives us confidence in the feasibility of using this testbed to investigate the flexible representation of speech in the STP. *Focus on the STP*. In this 2-year R21, we intentionally direct our primary focus to the STP because prior research[56-59] and our new sEEG pilot data (**Figure 3**) demonstrate a graded response to F0 and VOT acoustic dimensions that we can examine across experimental manipulations to listening context to understand flexible representation in speech processing, with theoretically-significant implications. Thus, our focus on STP is in the interest of delivering data to answer our seven theoretically-motivated hypotheses in the framework of a two-year R21 project. Nonetheless, it is important to note that the project will yield rich data from electrodes placed across cortex in the same subjects (**Figure 4**). We are enthusiastic about the secondary hypotheses and comparison of STP response to control electrodes that this will support to motivate future work founded on the results from this R21.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 02/28/2023

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	● Yes ❍ No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	● Yes ❍ No
Is the Project Exempt from Federal regulations?	❍ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Flexible Representation of Speech	Yes

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Flexible Representation of Speech

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	❍ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	❍ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- sEEG Implantation

2.2. Eligibility Criteria

Patients undergoing sEEG implantation to the STP for localization of epileptic foci or clinical language mapping are candidates for inclusion. Both epilepsy and brain tumor patients are candidates for inclusion. All participants will be fluent English speakers within the normal range on cognitive, speech-language, and hearing tests as tested by a speech language pathologist or neuropsychologist in advance of neurosurgery. Patient participants will have nonverbal IQ and receptive and expressive language scores within the normal range, normal or corrected-to-normal visual acuity, and normal hearing acuity in each ear (as determined during a full audiometric assessment), with no history of autism or ADHD.

2.3. Age Limits	Min Age: 15 Years Max Age: 25 Years
2.3.a. Inclusion of Individuals Across the Lifespan	2020_NIH_R21_IndividualsAcrossLifespan_final.pdf
2.4. Inclusion of Women and Minorities	2020_NIH_R21_PerceptualWeights_WomenMinorities.pdf
2.5. Recruitment and Retention Plan	2020_NIH_R21_PerceptualWeights_RecruitmentRete.pdf
2.6. Recruitment Status	Not yet recruiting
2.7. Study Timeline	2020_NIH_R21_PerceptualWeights_ProjectTimeline.pdf
2.8. Enrollment of First Participant	02/01/2021 Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN

This proposal includes participants from ages 15 to 25 years of age. This age range was picked because it overlaps with the typical young adults sampled by the larger behavioral literature on perceptual weight in speech perception. Additionally, we have access to this age range at our site of enrollment: Children's Hospital of Pittsburgh. Therefore, our sample will be a mix of children (<18 yrs) and adults (>18 yrs), by the NIH definition.

As described in the **Research Strategy** there is heterogeneity in baseline perceptual weights (**Figure 1e**) that is stable across time suggesting that differences reflect underlying processing rather than measurement fluctuation.[14] For example, even among listeners who consistently weight VOT more than F0 there is considerable variation in the extent to which individuals rely upon F0 in signaling contrasts like *beach* vs. *peach*.[15–19] Therefore, careful examination variation baseline perceptual weights can inform understanding of cortical response to speech. Heterogeneity is desirable. Our pilot results demonstrate that teenagers and young adults (mean age 20 years) exhibit a good degree of heterogeneity in perceptual weights (**Figure 1e**). This affords an opportunity to observe informative perceptual weight heterogeneity and to relate it to neural response. In the proposed project, the richness of this developmental period as a testing ground is amplified by pairing natural heterogeneity in baseline perceptual weights (Aim 1) with experimental manipulation of context in the same listeners, which evokes dynamic, flexible adjustments to perceptual weight (Aim 2, **Figure 1b, d**) to examine the relationship to neural response. The age range of our sample overlaps with the typical young adults sampled by the larger behavioral literature, and in our preliminary data (**Figures A, 1, 2, 5**).

The children included in this study will be undergoing clinically-necessary neurosurgery. Electrode implantation is planned based on clinical necessity by epileptologists not involved in the research, thereby protecting against surgeon-scientist conflict of interest. ***No electrode is implanted solely for research purposes.***

The research team has extensive experience acquiring data from children, adolescents, and young adults. All minor participants (< 18 years of age) will be required to provide assent in addition to parental consent. Children's Hospital of Pittsburgh (CHP) is a highly child-friendly environment. There is a sitting area for parents and families where they can view their child at all times, via closed circuit video capture.

INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

1. INCLUSION OF WOMEN AND MINORITIES

Recruitment of the patient group will consist of teenagers and young adults (ages 15-25 years) evaluated in the Children's Hospital of Pittsburgh epilepsy surgery program, with all efforts made to include equal numbers of males and females in the patient group. We do not expect gender to have any significant influence on any of the study results, and gender comparisons are not part of the study design; however, we cannot exclude the possibility of gender differences and so we will include gender as a covariate in our analyses.

Every effort is always made to include a diverse sample. We will also attempt to include minority participants among patients, reflecting the surrounding communities of the proposed research site. In Pittsburgh and Western Pennsylvania, the representation of minority populations is as follows: White/Caucasian 66.0%, Black/African American 26.1%, Asian 4.4%, American Indian/Alaskan Native ~1%, two or more races ~3%. Importantly, our studies are of equal benefit to males, females, and minority populations. Ethnic and racial data, using the Federal guidelines, will be collected for all participants.

2. INCLUSION OF CHILDREN

This proposal includes participants from ages 15 to 25 years of age. Therefore, our sample will be a mix of children (<18 yrs) and adults (>18 yrs), by the NIH definition.

As described in the **Research Strategy** there is heterogeneity in baseline perceptual weights (**Figure 1e**) that is stable across time suggesting that differences reflect underlying processing rather than measurement fluctuation.[14] For example, even among listeners who consistently weight VOT more than F0 there is considerable variation in the extent to which individuals rely upon F0 in signaling contrasts like *beach* vs. *peach*.[15–19] Therefore, careful examination variation baseline perceptual weights can inform understanding of cortical response to speech. Heterogeneity is desirable. Our pilot results demonstrate that teenagers and young adults (mean age 20 years) exhibit a good degree of heterogeneity in perceptual weights (**Figure 1e**). This affords an opportunity to observe informative perceptual weight heterogeneity and to relate it to neural response. In the proposed project, the richness of this developmental period as a testing ground is amplified by pairing natural heterogeneity in baseline perceptual weights (Aim 1) with experimental manipulation of context in the same listeners, which evokes dynamic, flexible adjustments to perceptual weight (Aim 2, **Figure 1b, d**) to examine the relationship to neural response. The age range of our sample overlaps with the typical young adults sampled by the larger behavioral literature, and in our preliminary data (**Figures A, 1, 2, 5**).

The children included in this study will be undergoing clinically-necessary neurosurgery. Electrode implantation is planned based on clinical necessity by epileptologists not involved in the research, thereby protecting against surgeon-scientist conflict of interest. ***No electrode is implanted solely for research purposes.***

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RECRUITMENT AND RETENTION PLAN

This document provides a detailed plan for execution of the Aims of this research project at the University of Pittsburgh and UPMC Children's Hospital of Pittsburgh. The organization of the document is as follows:

1. Engagement
2. Planning and timeline
3. Staff
4. Power & sample size
5. Recruitment strategies
6. Retention strategies
7. Coordinating the research project
8. Benefits to participation
9. Barriers to participation
10. Informational materials
11. Ensuring a diverse study sample
12. When the study has been completed

1. Engagement

- The research project will recruit patients from UPMC Children's Hospital of Pittsburgh and neurotypical subjects from the greater Pittsburgh community.
- MPI Abel has been at the [redacted] and UPMC Children's Hospital of Pittsburgh since July 2018, where he is an Assistant Professor of Neurological Surgery (with adjunct appointment in Bioengineering) and Surgical Director of the Pediatric Epilepsy Surgery Program.
- Together MPIs Holt and Abel will actively work throughout the tenure of this research project to maintain a high level of engagement. The team will have a standing bi-weekly meeting, or more frequently as needed, to review study progression, discuss roadblocks and develop strategies for moving forward.

2. Planning and Timeline

- Suitable IRB approvals are already in place [redacted] Modifications to the IRB protocol will be made upon funding to accommodate the full scope of the proposed research.
- Research tools for collection of pilot data, including button boxes, stimulus display monitors, sound booths and computer workstations are in place and functional in the MPIs' respective labs.
- The tasks and stimuli required for this project are in place, having been used to generate the pilot data described in the proposal. Protocol refinement for this study commence immediately Year 1 along with participant recruitment and enrollment. Participant recruitment and enrollment continue through Years 2, as needed.

	Milestones	Y1		Y2	
Aim 1	Personnel Recruitment	♦			
	Stimulus/paradigm development	♦			
	Pilot testing	♦			
	EEG set-up and piloting	♦	♦		
	Recruitment & testing		♦	♦	♦
	Analyses			♦	♦
	Dissemination		C		P
Aim 2	Pilot testing	♦			
	EEG set-up and piloting	♦	♦		
	Recruitment & testing – neurotypical & patient participants		♦	♦	♦
	Analyses			♦	♦
	Dissemination			C	P

3. Staff

- A Postdoctoral Researcher and Graduate student will be recruited in Year 1 of the study and will assist with aspects of engagement, study recruitment, IRB approval, data management, and research coordination.
- Regular (typically bi-weekly, although often more frequent) in-person meetings with the team will provide an opportunity to review past enrollment and retention, as well as discuss research findings and preparation of results for professional meetings and publication in peer-reviewed journals. These meetings will foster study organization across senior personnel and project staff/trainees.
- It is expected that some trainees or staff may be replaced during the tenure of the study. If this occurs, the replacement trainee or staffer will be recruited in anticipation of the end date of the exiting study personnel to ensure sufficient training time and knowledge transfer.

4. Power & Sample Size

- *Behavioral Effects*. Robust behavioral effects will support examination of their impact on neural representation. Using effect sizes from **Figure 2** data to estimate the sample size required for a predicted power of 0.8 (two-tailed alpha at .05) yields N=25.
- *Neural EEG Effects*. Our pilot EEG data with the same task/stimuli revealed robust effects with N=23 (**Figure A**), reassuring that N=25, estimated from the behavioral effect, is a reliable sample for EEG.
- *Neural sEEG Effects*. The SNR advantages of sEEG versus EEG suggest that this sample size (N=25) will be sufficient for sEEG measures, as well, especially as they will be utilized in a within-patient (and within-electrode) experimental design. sEEG studies are analogous to invasive neurophysiology in animal models and electrocorticography (ECoG) in humans, for which sample sizes are limited (sometimes to <10), but data collection from individuals is extremely rich. Our projected patient population sample size (N=25) will therefore provide a large enough sample size for a hold-out sample that would be useful in assessing the robustness of the proposed encoding and decoding models.
- Sample size will allow for robust and replicable effects.

5. Recruitment Strategies

- Patients will be recruited prior to sEEG implantation at UPMC Children's Hospital of Pittsburgh. Patients will be introduced to the project by MPI Abel prior to surgery and, when interested, consented by PI Abel.
- Any changes that are necessary to the recruitment materials, study protocol, additional study personnel, or consent forms will be accomplished through review by the IRB at the [redacted]
- Recruitment strategies will be assessed and approved by the [redacted] Institutional Review Board (with Carnegie Mellon University as an sIRB site). Participants under age 18 will assent to participation, with parent's informed consent.

Exclusion Criteria. Exclusion criteria include intellectual disability, abnormal epileptiform activity in the supratemporal plane, or a lack of fluent English comprehension/production. Patients are also excluded when preoperative cognitive testing demonstrates severe language or auditory specific cognitive dysfunction. Patients with autism or ADHD will also be excluded.

Inclusion Criteria. Patients undergoing sEEG implantation to the STP for localization of epileptic foci or clinical language mapping are candidates for inclusion. Both epilepsy and brain tumor patients are candidates for inclusion. All participants will be fluent English speakers within the normal range on cognitive, speech-language, and hearing tests as tested by a speech language pathologist or neuropsychologist in advance of neurosurgery.

Approach to Avoiding Conflicts of Interest. Research electrodes are placed solely for clinical purposes. As described elsewhere, targets for sEEG electrode exploration are chosen by the pediatric epileptology team who are not involved in this research and do not benefit from this research program. STP electrodes are commonly implanted to rule-out or establish the involvement of insulo-opercular cortex in temporal lobe epilepsy ('temporal plus' epilepsy), which has been shown to be a major determinant of failure after temporal lobe resection for epilepsy. Additionally, our IRB requires that a pediatric epileptologist caring for the research subject approves of all research activity on a daily basis to ensure that research will not obstruct clinical care or adversely impact the child's seizure threshold.

Projected Enrollment. Current caseload for MPI Abel at Children's Hospital of Pittsburgh will support successful recruitment of patient participants at the proposed sample size. Based on MPI Abel's neurosurgical enrollment with similar inclusion criteria across 2019 we anticipate no enrollment challenges across this two-year project (see **Table I**). Approximately 70% of his 2019 cases involved electrode placement in the STP. The planned study enrollment is realistic given the clinical volume and research history at UPMC Children's Hospital of Pittsburgh. However, should recruitment be lower or should attrition rates be higher than anticipated, we will extend the period of recruitment further into Year 2 than anticipated.

Fourteen patients were enrolled in research during the last 12 months at CHP, of whom 12 had electrodes in the STP. This period included 2 months of halted elective surgery due to the pandemic. In the next two months, we anticipate

Table I. Estimates for two years of data collection based on 2019 enrollment.

	# Patients	# Electrodes
L HG	14	14
R HG	12	12
L aSTP	12	12
R aSTP	10	10
L pSTP	14	18
R pSTP	12	16
L aSTS	12	22
R aSTS	10	20
L pSTS	12	12
R pSTS	8	14

a: Anterior; **p**: Posterior; **HG**: Heschl's Gyrus, **STP**: Superior Temporal Plane (relative to HG); **STS**: Superior Temporal Sulcus

enrolling three patients with planned STP coverage. On this basis, we do not expect difficulty achieving the enrollment numbers for this proposal.

6. Retention Strategies

- Studies with sEEG occur in the acute setting when sEEG electrodes are implanted and patients are hospitalized. Optimizing patient comfort will be important for facilitating retention during this short period of implantation. Patient comfort is essential.
- Throughout the experiment, the researchers repeatedly check in with the participant to ensure they are comfortable, providing regular breaks between block/tasks with additional breaks and snacks as needed. If the participant does not appear comfortable at any time, even if they do not state it aloud, we terminate the experiment immediately. While we do not anticipate stressful reactions using our protocols, if they occur, we would offer comfort by offering other activities the participant enjoys, including snacks, reading a book, videos/games, watching part of a movie, etc., to help the participant relax. Our primary concern if a participant were to be upset is to ensure the participant is calm and happy before the experimenter leaves the patient.
- Retention will be monitored by examining the percentage of participants who complete a first session who go on to complete all sessions. If average retention levels drop from our expectations, determined through quarterly reviews by the research team, the research team will determine a new course of action to encourage greater retention and participation levels. We have noticed that patient participation is higher now that patients are remunerated $15/hr for their participation.

7. Coordinating the Research Project

- MPI Abel's laboratory at UPMC Children's Hospital of Pittsburgh will serve as the coordinating center for all aspects of this study. As noted above, the entire research team (MPIs, postdoctoral associate, graduate student) will have quarterly meetings to discuss the research project as a whole. At least one of the MPIs will meet at least weekly with each member of the research team. The MPIs will have bi-weekly meetings, or more frequently as needed, to discuss project progress. Electronic communication (e.g., email, text messaging) will be ongoing throughout the project.

8. Benefits to Participation

- The principal benefit for enrolling in this study, from the perspective of potential participants, is that they will have the opportunity to advance scientific knowledge. Many participants have noted, upon participating in our research team's similar studies, that they perceive a benefit to be contributing to knowledge and science, with the hope that the knowledge gained may be used in the future to help others.
- Care is taken to ensure that participation in these research studies is as easy as possible for participants.
- Participants are compensated $15/hr for research participation.

9. Barriers to Participation

- For sEEG patients, medical factors (fatigue, seizures, surgical pain) can sometimes be barriers to research participation. As a leader of the surgical team, PI Abel is intimately aware of these concerns and works to mitigate these barriers when possible.
- Should we encounter barriers, the research team will meet to consider adaptations to the protocol that can meet the scientific needs while broadening participation.

10. Informational Materials

- All participants (or, for minors, their parents) will be provided a detailed explanation of all aspects of the project, encouraged to ask questions, and given a copy of the written consent form that describes the experiment for a lay audience. The information has been developed with a wide audience in mind, and wide literacy levels, indicating the components of participation. Minor children will give their assent to participate in the study.
- Patients and families who are interested can request to receive information about the study outcomes written for a lay audience.

11. Ensuring a Diverse Study Sample

- Recruitment into the study follows consecutive enrollment for participants meeting the eligibility criteria.

- sEEG patients will be recruited from neurosurgical patients who are undergoing evaluation and treatment for epilepsy or brain tumor, and who require chronic (i.e. >7 d) sEEG implantation and recording of the temporal lobe for seizure localization or brain mapping.
- Every effort will be made to recruit a diverse sample from within this patient population. We attempt to include minority participants among patients, reflecting the surrounding communities of the proposed research site. In Pittsburgh and Western Pennsylvania, the representation of minority populations is as follows: White/Caucasian 66.0%, Black/African American 26.1%, Asian 4.4%, American Indian/Alaskan Native ~1%, two or more races ~3%. Importantly, our studies are of equal benefit to males, females, and minority populations. Ethnic and racial data, using the Federal guidelines, will be collected for all participants.
- All efforts made to include equal numbers of males and females in the patient group. We do not expect gender to have any significant influence on any of the study results, and gender comparisons are not part of the study design; however, we cannot exclude the possibility of gender differences and so we will include gender as a covariate in our analyses.
- The research team aims to have a diverse group of trainees and staff working on the study (and related studies), including racial and ethnic minorities and a gender balanced group of individuals. The research team will have bi-annual meetings with all trainees and staff to ensure that everyone is following best practices when interacting with study participants, and that all team members maintain a high-level of sensitivity to cultural, racial and ethnic differences, as well as socioeconomic disparities.

12. When the Study has been Completed

- Participants will be given debriefing information including the MPIs' email and office phone number, as well as contact information for the IRB.
- Additionally, participants will have the opportunity to sign up for study updates including publication or presentation of study findings. This ensures that participants understand they can still reach out to the study team to learn about results even after they are no longer actively participating in the research.

PROJECT TIMELINE

The timeline initiates immediately upon funding. In the chart below Aim 1 and Aim 2 proceed in parallel throughout the project, with recruitment and testing proceeding into Year 2.

sEEG, EEG, and behavioral data will be collected in patient populations by the PIs and study personnel at Children's Hospital of Pittsburgh throughout the project. Data will be analyzed continuously and added to the larger dataset at quarterly intervals. Preparation of research products corresponding to core and secondary hypotheses will initiate in Year 1. Each Aim is expected to yield at least two major publications, and additional shorter papers corresponding to interim findings appropriate for conference proceedings.

Table 1. Project Timeline C = Conference, P = Publications

	Milestones	Y1		Y2	
Aim 1	Personnel Recruitment	♦			
	Stimulus/paradigm development	♦			
	Pilot testing	♦			
	EEG set-up and piloting	♦	♦		
	Recruitment & testing		♦	♦	♦
	Analyses			♦	♦
	Dissemination		C		P
Aim 2	Pilot testing	♦			
	EEG set-up and piloting	♦	♦		
	Recruitment & testing – neurotypical & patient participants		♦	♦	♦
	Analyses			♦	♦
	Dissemination			C	P

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	UPMC Children's Hospital of Pittsburgh

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : Anticipated Enrollment

2. Using an Existing Dataset or Resource* : ❍ Yes ● No

3. Enrollment Location Type* : ● Domestic ❍ Foreign

4. Enrollment Country(ies): USA: UNITED STATES

5. Enrollment Location(s): UPMC Children's Hospital of Pittsburgh

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	9	8	1	1	19
More than One Race	0	0	0	0	0
Total	12	11	1	1	25

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	2020_NIH_R21_PerceptualWeights_HumanSubjects_f.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	2020_NIH_R21_PerceptualWeights_sIRB_final.pdf
3.3. Data and Safety Monitoring Plan	2020_NIH_R21_PerceptualWeights_DataSafetyMonit.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	● Yes ❍ No
3.5. Overall structure of the study team	2020_NIH_R21_PerceptualWeights_StudyTeam_final.pdf

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects

a. Human subjects involvement, characteristics, and design. Our scientific premise is that next-generation models of human cortical speech processing must account for adaptive plasticity -- the dynamic, flexible mapping of speech input to perception. Our approach marries behavioral manipulation of listening context in speech categorization with simultaneous EEG and sEEG measurement of neural response. Our pilot data establish the behavioral (**Figures 1, 2**), EEG (**Figure A**), and sEEG (**Figure 3**) approaches, all of which have been reviewed by Carnegie Mellon University and/or [redacted] Institutional Review Boards.

Table I. Annual estimates based on 2019 enrollment.

	A	B
L HG	14	14
R HG	12	12
L aSTP	12	12
R aSTP	10	10
L pSTP	14	18
R pSTP	12	16
L aSTS	12	22
R aSTS	10	20
L pSTS	12	12
R pSTS	8	14

Column A: Patients; Column B: Electrodes. (**a**: Anterior; **p**: Posterior; **HG**: Heschl's Gyrus, **STP**: Superior Temporal Plane (relative to HG); **STS**: Superior Temporal Sulcus)

Recruitment and Sample: Patient participants will be recruited from pediatric patients who undergo implantation of sEEG electrodes at CHP. This will predominantly (95% based on previous enrollment) be epilepsy patients undergoing sEEG implantation for localization of epileptic foci, but occasionally brain tumor patients who are not candidates for awake craniotomy undergo sEEG implantation for localization of language function. Our participants across two years will include 25 patient participants, ages 15-25 years who are undergoing evaluation and treatment for epilepsy or brain tumor, and who require chronic (i.e. >3 d) sEEG implantation and recording of the temporal lobe for seizure localization or brain mapping. Based on the historical volume of epilepsy surgery at CHP and the volume from the PI's clinical practice at CHP, this level of participant recruitment is highly feasible (see **Table I**). Please see **Inclusion of Women, Minorities, and Children** and **Approach** for a full justification of the scientific rationale for examining this age range.

Exclusion Criteria.
In general, patients with significant medical or neuropsychological impairment, who would be unable to participate for the proposed research, will not be considered for inclusion in the proposed studies. Exclusion criteria include intellectual disability, abnormal epileptiform activity in the supratemporal plane, or a lack of fluent English comprehension/production. Patients are also excluded when preoperative cognitive testing demonstrates severe language or auditory specific cognitive dysfunction. Patients with autism or ADHD will also be excluded.

***Inclusion Criteria*.** Patients undergoing sEEG implantation to the STP for localization of epileptic foci or clinical language mapping are candidates for inclusion. Both epilepsy and brain tumor patients are candidates for inclusion. All participants will be fluent English speakers within the normal range on cognitive, speech-language, and hearing tests as tested by a speech language pathologist or neuropsychologist in advance of neurosurgery. Patient participants will have nonverbal IQ and receptive and expressive language scores within the normal range, normal or corrected-to-normal visual acuity, and normal hearing acuity in each ear (as determined during a full audiometric assessment), with no history of autism or ADHD.

The population in this project will be recruited equally from both sexes and all ethnic or racial groups (see **Inclusion of Women, Minorities, and Children**).

Power: Robust behavioral effects will support examination of their impact on neural representation. Using effect sizes from **Figure 2** (**Approach**) data to estimate the sample size required for a predicted power of 0.8 (two-tailed alpha at .05) yields N=25.This leaves open the issue of power for neural measures. Our pilot EEG data with the same task/stimuli revealed robust effects with N=23 (**Figure A, Introduction**), reassuring that N=25 is a reliable sample for EEG. The SNR advantages of sEEG versus EEG suggest that this sample size will be sufficient for sEEG measures, as well, especially as they will be utilized in a within-patient (and within-electrode) experimental design. sEEG studies are analogous to invasive neurophysiology in animal models and electrocorticography (ECoG) in humans, for which sample sizes are limited (sometimes to <10), but data collection from individuals is extremely rich. Our sEEG pilot data demonstrate that each of the 7 patients examined exhibited significant graded high-gamma activity across VOT and F0 dimensions for channels on an electrode placed along the STP.

Retention. Our retention plan involves ensuring that participants are comfortable before and during sessions. We will offer breaks and snacks as needed. Please see **Recruitment and Retention Plan** for details.

Confidentiality: Data will be acquired from patient participants at Children's Hospital of Pittsburgh (CHP), under the direction of MPI Abel. All data will be obtained directly from patients and/or their caregivers and stored at CHP, respectively. Only consent forms will contain participant names. All other forms will be labeled by an assigned participant identification number. One digital form will contain the participant's name and assigned participant identification number. This form will be individually locked, only accessible by the MPIs and trained research personnel. It will be stored on a locked computer. All participant files will be stored in a locking file cabinet or on a locked computer accessible only by researchers affiliated with the project.

Neurosurgical Protocol*:* In brief, individual electrode trajectories are planned using a 3D MPRAGE post-contrast MRI fused to a 3D CT angiogram (to ensure avascular trajectories). Robot-assisted (Meditech ROSA) stereotactic implantation of each planned trajectory is then performed in the operating room under general anesthesia, per clinical protocols. Electrode localization is confirmed using intraoperative CT imaging (Medtronic O-Arm). After surgery, patients typically spend one night in the pediatric intensive care unit and then transfer to the epilepsy monitoring unit the following day. Once feeling well (1-2 days postop) patients may consent/assent to participate.

Behavioral Protocol*:* The acoustic stimuli have been extensively tested in MPI Holt's prior research[25-27,29], as in pilot data in **Figures A, 1** and **2**. They are derived from natural speech, and subtly manipulated to parametrically vary across the VOT and F0 dimensions. During the post-op period, patients will complete self-paced blocks of trials that simply require listening to a sound diotically over insert earphones and deciding whether the initial consonant is a [b] or a [p]. To facilitate response, we will use minimal pair English words (*beach* vs. *peach,* e.g.) that can be illustrated. Patients will tap a button to indicate which picture matches the word heard. Each patient will categorize stimuli across the 2-d VOTxF0 acoustic grid for clear speech (Aim 1, **Figure 1a**) and speech-in-noise (Aim 2, **Figure 1c**) and across the Canonical-Reverse block structure that introduces an artificial accent in the DBSL paradigm (Aim 2; **Figure 2a**). All manipulations are within-patient, lending considerable statistical power to test our predictions. Crucially, the same *Test* stimuli are present in each block (blue/green symbols, **Figure 2a**), providing a 'gold standard' against which to examine how neural response to identical stimuli is modulated as a function of listening contexts that robustly influence perceptual weights in behavioral tasks. These methods are classified as minimal risk by our IRB. Our approach is to make the task as interesting and engaging as possible to make patient participants comfortable.

b. Sources of Materials. The neurophysiological and behavioral data acquired in these studies is specifically and only used for research purposes. Behavioral and neurophysiologic data will be collected as well as personal information from answers on questionnaires. Only the MPIs and research personnel who are actively working on this project will have access to data collected for this project. All researchers have completed the [redacted] and NIH Protection of Human Research Protection computer-based training programs. All data will be stored in a locking file cabinet or on servers protected by a password, which are accessible only by password protected computers. All electrophysiological and behavioral data will be labeled with a participant identification number. The link between participant name and identification number will be housed in one electronic document that is individually password protected (a different password from lab computers and servers). Only the trained researcher personnel will have access to this file.

c. Potential Risks. Participants will incur minimal additional risk by participating in this study. ***Electrode implantation strategies for localizing epileptic foci are based solely on each patient's clinical needs and are not dictated by research***. Furthermore, surgical technique would be the same for research and non-research participants (there will be no special "research electrodes" implanted for the purpose of this study). The risks of electrode implantation are discussed with the parents and patients during the surgical consent process, which is completely separate from the research, consent process. STP electrodes are commonly implanted to rule-out or establish the involvement of insulo-opercular cortex in temporal lobe epilepsy ('temporal plus' epilepsy), which has been shown to be a major determinant of failure after temporal lobe resection for epilepsy.

On that basis, while electrodes are not implanted solely for research purposes, we will frequently enroll participants with STP electrode coverage as this region is important for localization of insulo-opercular seizure involvement in temporal lobe epilepsy. Please also see **Data Safety and Monitoring Plan**.

Our neurosurgical research protocol is currently approved by the University of Pittsburgh IRB and we are actively enrolling research subjects on highly similar protocols.
We have had no research related adverse events.

Psychological risks are also minimal since no pressure or stress is applied at any time, or specifically as a result of performance on the tasks. The MPIs have extensive experience acquiring behavioral and brain data from hundreds of participants, including from vulnerable populations, and we have found that the vast majority of participants are comfortable with our procedures. Adolescents and parents, and adults (> 18 years) are informed that they may stop participation at any time. Throughout the experiment, the researchers repeatedly check in with the participant to ensure they are comfortable, providing regular breaks between block/tasks with additional breaks and snacks as needed. If the participant does not appear comfortable at any time, even if they do not state it aloud, we terminate the experiment immediately. While we do not anticipate stressful reactions using our protocols, if they occur, we would offer comfort by offering other activities the participant enjoys, including snacks, reading a book, videos/games, watching part of a movie, etc., to help the participant relax. Our primary concern if a participant were to be upset is to ensure the participant is calm and happy before the experimenter leaves the patient.

There are no social or legal risks.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent. Patient participants will be recruited from pediatric patients who undergo invasive localization of epileptic foci at the CHP and are paid $15/hour.

Patients and parents will be given extensive explanations about the potential risks and benefits of the proposed research during the research consent process. Patients and parents will be told about the aims of the study and about the confidentiality of the data obtained. It will be made clear to patients and parents that their participation is completely voluntary at all stages and is distinct from clinical care. Each patient (or their parent) is free to disengage the patient from research involvement at any time.

Experimenters will obtain consent by asking patients and parents or legal guardians to sign consent forms after answering any questions and addressing any concerns that they may have. Patients <18 years will be read an age-appropriate assent form aloud and any questions will be answered before obtaining written assent via the Child Assent Form. Parents will be required to read and sign a separate Parent Consent Form.

All personnel involved in any aspect of the research program are certified as completing the University of Pittsburgh and the NIH Protection of Human Research Subjects computer-based training programs.

b. Protection Against Risk. Physical risks will be minimized using standard laboratory and equipment procedures whose main elements are outlined above. No adverse effects specific to the proposed research that would require medical intervention are expected. Potential adverse effects of sEEG specific to the surgical process, which is completely separate from the research process.

For the proposed studies, risks of electrical shock during EEG recording are minimized by proper electrical grounding of participants and by isolation of electrical recording and stimulation equipment from ground.

Participants' records are kept completely confidential under control of the investigators and associates. A participant's data are only identified by a code and could not be used adversely to his or her interests.

If a participant becomes upset at any time during a session, the task will be discontinued immediately and every effort will be made to comfort the participant, with the parent's help, and engage him/her in an activity that is not distressing (for example, playing a game) so that s/he will leave with a positive experience. In all cases participants are informed repeatedly that they can decide to halt participation at any time.

3. Potential Benefits of the Proposed Research to the Subjects and Others
There will be no direct benefit to the patient beyond payment for participation in the experiment ($15/hr). The research described holds the promise of contributing to the refinement of our understanding of the neurobiological basis of speech processing.

Since the risks to the participants are very low, the risk-benefit ratio seems quite acceptable in light of the potential for improving understanding of the neurobiological basis of speech processing.

4. Importance of the Knowledge to be Gained
The proposed research will increase understanding of the neural basis of speech processing. The findings from this study will enhance knowledge regarding foundational auditory processes available to speech communication. Long-term implications of this research include the potential for translational contributions to tackling the many communication disorders that impact listeners.

The research risks to the participant are very low; therefore, the risk-benefit ratio seems quite acceptable in light of the potential for improving models of auditory processing as well as potential for refining interventions targeting adolescents.

sIRB PLAN

This study will comply with the NIH Policy on the Use of sIRB for Multi-Site Research. The [redacted] Institutional Review Board (IRB) has agreed to serve as the sIRB of record for human subjects research under this grant. Carnegie Mellon University (CMU), the participating site, will rely on the proposed sIRB and any sites added after award will rely on the sIRB. [redacted], the proposed sIRB will maintain records of the reliance agreements and the communication plan. The participating sites will, prior to initiating the study, sign an authorization/reliance agreement that will clarify the roles and responsibilities of the Reviewing IRB and participating sites.

We will comply with the NIH Policy on the Use of sIRB for Multi-Site Research. Awardees will comply with the policy pursuant to the sIRB plan.

The [redacted] team will be responsible for ensuring ongoing communication with all participating sites via regular in-person meetings and electronic communication throughout the study. Key communication points will occur to:

- Disseminate IRB determinations and IRB-approved documents
- Educate study teams regarding the approved study and amendments to the study
- Alert study teams to problems that may affect the conduct of the study or the rights and welfare of research participants, such as unanticipated problems.
- Inform study teams of any changes in study status or new information
    - Facilitate submissions to the Reviewing IRB, including:
    - Inclusion of site-specific requirements in consent documents
    - Identification of any variability in study implementation across sites that must be communicated to the University of Pittsburgh IRB
    - Collection of information from participating sites to include in continuing review reports to the [redacted] IRB
    - Site-specific amendments
    - Personnel updates (as required by the [redacted] IRB)
    - Reportable events (e.g., noncompliance, unanticipated problems)
    - Closure reports
    - Ensure revisions to applicable conflict of interest management plans are provided to the [redacted] IRB

This project will use the SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement (SMART IRB Agreement) to support single IRB review across [redacted] and Carnegie Mellon University. SMART IRB is an online reliance platform designed to streamline and advance reliance through a common IRB authorization agreement. The SMART IRB Agreement outlines the responsibilities of all Participating Institutions, the Reviewing IRB, and Relying Institutions, and provides templates for communication between the Reviewing IRB and Relying Institutions. All sites in this study are members of SMART IRB and will indicate reliance and willingness to invoke the SMART IRB agreement prior to IRB review.

DATA SAFETY AND MONITORING PLAN

The MPIs will assume mutual responsibility for data safety and monitoring. The data monitoring and management plan covers all aspects of this project.

1. Safety in a Neurosurgical Context: Clinical Rationale

Electrodes trajectories are chosen purely on the basis of clinical necessity as determined by pediatric epileptologists that are not involved in the research protocols. This includes placement of the STP electrodes that are utilized for the purposes of this study. Our STP electrode trajectories mimic those that have been used at experienced sEEG centers in Europe for over 50 years, which have standardized trajectories to explore the 1) anterior STG, planum polare, and anterior insula (electrode 'T'), 2) middle STG, Heschl's gyrus, and posterior insula (electrode 'U') and 3) posterior STG, planum temporale, and the posterior cingulate (electrode 'V'). These trajectories are used at experienced sEEG centers across France, Italy, and at some centers in the United States as they maximize the number of brain regions examined by single electrode trajectories in a safe and established manner. Figure 1 depicts all of the standard electrode trajectories we use and provides an example of a de-identified schematic implantation plan formulated by our pediatric epileptology team (who are not involved in the research).

Clinically, STP electrodes are often placed for two reasons: 1) to rule-out or establish temporal plus epilepsy (temporal lobe seizures that spread rapidly from the mesial temporal lobe to the insulo-opercular region; Barba et al. 2007; Barba et al. 2016) and 2) for clinical language stimulation mapping with sEEG electrodes. As outlined by Barba et al. (2016), temporal lobe epilepsy patients with temporal plus epilepsy are 5x more likely to not be seizure free after epilepsy surgery, so exploration of the insulo-opercular region is essential when clinical evaluation implicates temporal plus epilepsy. Furthermore, since the rationale for exploration of the STP and insulo-opercular region is to rule-out temporal plus epilepsy or perform language mapping, often the interictal activity from STP electrodes is normal (though STP electrodes can be removed from analysis when interictal abnormalities preclude research investigation of normative brain function).

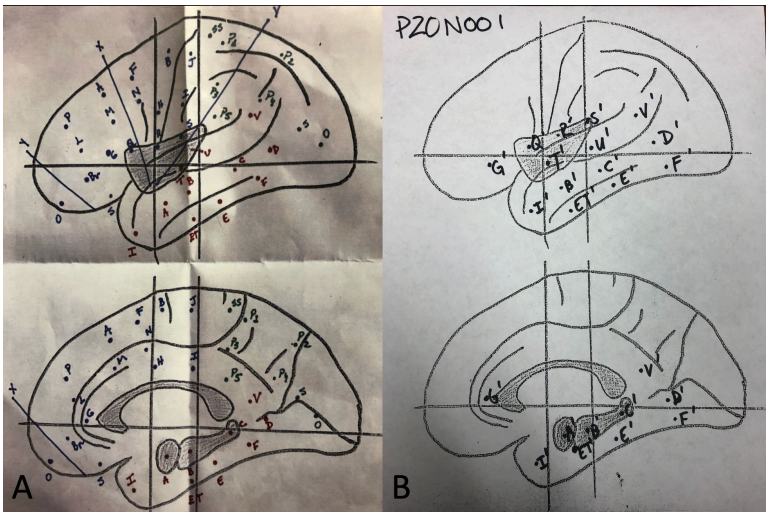

Figure 1. Clinical sEEG electrode planning schematics. **(A)** Standard electrode trajectories used at UPMC Children's Hospital of Pittsburgh. **(B)** Example of electrode schematic provided by pediatric epileptology team utilizing standard clinical electrode trajectories.

2. Safety in a Neurosurgical Context: Avoiding Clinician/Scientist Conflict of Interest

Electrode trajectories are proposed entirely by the pediatric epileptology team on the basis of clinical hypotheses of the localization of each individual's epileptogenic zone. PI Dr. Abel's clinical role is the safe implantation of sEEG electrodes once the pediatric epileptology team has provided a schematic plan (see **Figure 1b**) for what brain regions each sEEG electrode should explore.

3. Expected data. This project will produce the following types of data: interview responses from background questionnaires from participants to assess eligibility, behavioral data standardized and non-standardized tests, questionnaires, psychoacoustic/perceptual tasks, scalp electroencephalography (EEG), and intracerebral stereoelectroencephalography (sEEG).

- Interview responses will record basic demographic information. Responses will be entered in a password protected and encrypted file on a secured laboratory computer.
- Experimental behavioral data will consist of keypress responses made during the course of the experiment using E-prime, Psychophysics Toolbox 3 in Matlab, Unity, tablet/online videogames, or similar. Custom

analysis scripts will be used to summarize the data. All data is stored with a study ID, independent of participant identity.
- Electrophysiology data will consist of auditory cortical responses evoked via sound and recorded with a Brain Vision actiCHamp system.

All data will be de-identified at the time of collection to a pre-assigned subject ID code. An encrypted and password protected spreadsheet will be the only recorded link between specific subjects and their IDs. This is the only recorded link between participant identity and their identification number.

All interview responses will be recorded into electronic spreadsheets and paper notes will be stored in a locked file cabinet in the MPIs' laboratories. All electronic data (behavioral data files, EEG files, etc.) will be stored on a secured computer server in the MPIs' laboratory and backed up onto the servers at the CHP. This way, two full copies of all of the recorded data are preserved in two separate locations at all times. Files and folders will be encrypted and password protected.

4. Period of data retention. All data will be for a minimum of 7 years after completing the project.

5. Data publication. The investigators will promptly prepare and submit all significant findings from work conducted under the award for publication, with authorship that accurately reflects the contributions of those involved and support from NIH. The investigators will pursue open access approaches to publication (as budgeted) and will deposit manuscripts in PubMed Central (PMC), which may be accessed online.

6. Standards to be used for data and metadata format and content. Data and metadata will be stored using the simplest possible formats to assure data longevity. The lowest level of individual trial-level data will be available in a de-identified format. Each type of data will be linked to detailed notes regarding how the data were generated, the metadata, and the analytical methods used to summarize and analyze them. During the conversion process, any potential identifying information is stripped from the file so that all data made for analysis is anonymous.

7. How the data are accessible and data-sharing practices and policies. All data will be stored in the MPIs' laboratories. The MPIs will maintain the datasets privately until publication of their results. Once published, all datasets will be opened to secondary research by both internal and external collaborators. Should the MPIs leave the institution, or should there be a change to their roles and responsibilities, the senior personnel remaining at University of Pittsburgh will assume responsibility for data management.

8. Policies and provisions for re-use, re-distribution, and production of derivatives. During the project lifecycle, data set access will be restricted to the core research team. This includes the MPIs and lab personnel. At the conclusion of the project, the EEG datasets and related experimental materials will be made public and accessible through a publicly available web server and/or through sources such as NeuroVault (depending on analysis type). In addition, all analysis scripts built as part of this project will be made publicly available via open source code development websites. Attracting researchers to perform secondary analysis on these data sets will occur on a lab-by-lab basis, based on presentation of works in scientific publications and professional meetings.

Once published, datasets may be opened to secondary research by both internal and external collaborators by submission to data sharing websites. There is a data-sharing clause in our IRB consent forms that participants can opt out of if desired.

9. Reusability of Data. Research groups who are likely to be interested in using these data include researchers who study auditory cognitive neuroscience and speech processing.

10. Ethics and Protection of Privacy - Human Subjects Research. All data collected or analyzed will be solely for research purposes and for the proposed studies. During the project lifecycle, dataset access will be restricted to the core research team. This includes the MPIs' senior lab personnel (postdocs, lab manager, and graduate

students) and IRB-approved collaborators. Extensive precautions are in place to ensure subject privacy and maintain confidentiality of the data. These precautions include restricted identification of subjects by de-linking their data ID number to any identifiable information. Only research staff will have access to this information. In addition, all data will be stored on encrypted and password protected servers behind the University of Pittsburgh firewall.

11. Responsibility. All research personnel will be instructed on data collection, data analysis, data archiving and data sharing by the MPIs. The MPIs and the first author of subsequent publications will be responsible for archiving the data. The MPIs will oversee the archival process and will ultimately be responsible for data archiving and sharing.

12. Intellectual Property Rights. All intellectual property, including data, generated under this project will be managed in accordance with institutional policies.

13. Safety Monitoring. The protocols used in the present studies are all classified as “Greater than Minimal Risk” by the University of Pittsburgh Institutional Review Board. This classification is because our IRB enables us to perform brain stimulation experiments, but no such experiments are part of this proposal. The occurrence of any adverse events associated with this study and its procedures, as well as any changes in risk level will be monitored by the MPIs of this study. Participants will be monitored for the duration of their participation in the proposed studies. The investigators of the study will promptly report to the IRB any unexpected adverse reactions of serious severity or unexpected adverse reactions of moderate or greater severity that are associated with the research and observed in conjunction with the conduct of this research study. Non-fatal or non-life-threatening adverse reactions associated with this research study will be reported to the IRB as soon as possible and no later than 10 days. Any major disputes between the research investigators and a research participant, or between research investigators, will be promptly reported to the IRB. The study investigators will closely monitor all participants for any such adverse events. The study investigators will meet annually to review the occurrence of any adverse events, as well as discuss recruitment, confidentiality, and/or relevant information that may impact on the safety of study participants and ethics of the research study, participant confidentiality, and data collection and data analysis issues pertinent to this study. A summary detailing the frequency of data and safety monitoring and the information gathered from these meetings will be submitted to the IRB in writing at the time that the research study is submitted for renewal.

These experiments will provide basic knowledge that, in addition to developing theories of speech processing, may extend to communication disorders, phonological disorders, developmental disorders such as autism, hearing impairment, and assistive technologies such as hearing aids and automatic speech recognition. The research involves minimal risk.

14. References

Barba, C., et al. "Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal ‘plus’ epilepsies." *Brain* 130.7 (2007): 1957-1967.

Barba, Carmen, et al. "Temporal plus epilepsy is a major determinant of temporal lobe surgery failures." *Brain* 139.2 (2016): 444-451.

STRUCTURE OF THE STUDY TEAM

Multiple PI Leadership Plan

PI Abel and PI Holt have established an organizational structure for the conduct of all aspects of the research. Although this is a new research team, there is a clear structure that has already demonstrably produced excellent results, as exemplified by the preliminary data collected over the last year. Consistent with team-based science

PI Abel arrived in Pittsburgh, PA last year to join the Children's Hospital of Western Pennsylvania (Neurological Surgery) which is in the vicinity of Carnegie Mellon University, where PI Holt directs her laboratory. Abel and Holt have collaborated closely in developing the scientific premise and the research plan described in the proposal. The work draws synergistically from their complementary research expertise. The collaboration is supported by the geographic adjacency of their laboratories (a short drive or bus ride). Weekly joint research meetings through the Pittsburgh Cognitive Auditory Neuroscience research network and meetings specific to this project will foster continued intellectual exchange and co-mentorship of junior members of the research team. The MPIs will be involved in all scientific aspects of the proposed project; decision-making will be joint. They will collaborate to achieve the specific aims and to ensure that both data collection sites comply with US laws, DHHS and NIH policies. Both sites will have human participant research approvals to cover the scope of the proposed projects, as detailed in the sIRB Plan.

Leadership: The MPIs will oversee the project jointly, with PI Abel serving as the NIH contact who will assume, with his institution, [redacted] the fiscal and administrative management responsibilities. The MPIs will share the responsibility for the scientific direction of the research, its progress, theoretical interpretation, and dissemination. The MPIs will jointly oversee the entire Research Program, the implementation of the scientific agenda and the leadership plan as equals.

Communication: Communication among the MPIs occurs at least bi-weekly by electronic conference/phone or in person; there is more frequent contact by email, online messaging, and electronic file transfer as dictated by project demands. In these meetings, the MPIs discuss project progress, student training, experimental design, integration of the research efforts, data analysis, manuscript preparation and administrative responsibilities. Additionally, key personnel and students within the MPIs' laboratories maintain regular contact about research progress through joint lab meetings as well as through electronic data sharing, email, meet-ups at local events, and phone conversations. The MPIs will assume the responsibility for informing the other about research progress in his/her own laboratory.

Conflict Resolution: Should a conflict arise the MPIs shall meet to attempt to resolve any dispute. If this meeting fails to resolve the dispute, the appropriate Department administrators from the MPIs' home departments will attempt to settle the dispute in good faith. However, if the Department administrators fail to resolve the conflict within 30 business days, an impartial arbitration committee will be formed consisting of an impartial senior executive and a third impartial member mutually agreed upon by both the MPIs. This committee will assist in resolving the dispute. No members of the arbitration committee will be directly involved in the proposed research or in the disagreement.

Data Sharing will be open between the laboratories. The MPIs will share their respective research results with the each other, key personnel, staff and students. To facilitate data sharing, the MPIs have established a policy of electronic data sharing that serves to support the ongoing collaboration.

Publication Authorship will reflect the relative scientific contributions of the MPIs, key personnel, and students.

Any **Intellectual Property** developed as part of the proposed project will be negotiated by the Technology Transfer Offices at [redacted] and Carnegie Mellon University to create a cross-institution agreement. In the event of such a negotiation, an Intellectual Property Committee of representatives from each institution will coordinate to protect intellectually property developed by the MPIs according to policies established in the agreement.

Should there be a **Change in MPI Location**, attempts will be made to transfer the relevant portion of the grant to the new institution.

A **Post-doctoral Scholar** will be involved in the research. Based at Children's Hospital, s/he will be involved in all aspects of the project, providing continuity. S/he will have full access to training in the PIs' laboratories, as well. S/he will spend time training with each PI, which will further support project continuity across sites. The post-doctoral scholar will be involved in all aspects of the work. The MPIs will work with the post-doctoral scholar to develop a post-doctoral mentoring plan, including an individual development plan. A **PhD student** based in PI Holt's laboratory will be involved in all aspects of the project, with mentoring by the senior personnel with primary responsibility by PI Holt with substantial input from PI Abel. A part-time **Clinical Research Coordinator** will assist with testing patients under the supervision of PI Abel.

Section 4 - Protocol Synopsis (Study 1)

4.1. Study Design

4.1.a. Detailed Description

Epilepsy or brain tumor patients who undergo sEEG implantation for clinical purposes are approached for potential participation in this research study. Consented patients then participate in an array of behavioral tasks during sEEG recording from the STP.

4.1.b. Primary Purpose: Basic Science

4.1.c. Interventions

Type	Name	Description
Other	Behavioral Tasks	Behavioral tasks are administered during sEEG recordings to examine changes in brain activity.

4.1.d. Study Phase: N/A

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.1.e. Intervention Model: Single Group

4.1.f. Masking ❍ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.1.g. Allocation: N/A

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	sEEG Recording	Acute	Neural signals are acquired from sEEG recordings during behavioral tasks that vary F0 and VOT.

4.3. Statistical Design and Power: 2020_NIH_R21_PerceptualWeights_StatisticalDesi.pdf

4.4. Subject Participation Duration: Up to 7 days after sEEG implantation.

4.5. Will the study use an FDA-regulated intervention? ❍ Yes ● No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.6. Is this an applicable clinical trial under FDAAA? ❍ Yes ● No

4.7. Dissemination Plan: 2020_NIH_R21_PerceptualWeights_DisseminationPl.pdf

STATISTICAL DESIGN AND POWER ANALYSIS

Statistical Design, Power and Analytic Approach. We will test neurosurgical patients (ages 15-25 years) undergoing evaluation and treatment who require chronic (>7 d) sEEG implantation and recording of the temporal lobe for seizure localization or brain mapping. One set of behavioral tasks, and corresponding electrophysiological measures, will allow us to address Aim 1. Another will address Aim 2. Patient permitting, our goal is to have the same patient complete all tasks. All participants will undergo neuropsychological tests and will have detailed history/demographic information as part of their clinical battery.

Power and Sample Size. Robust behavioral effects will allow examination of perceptual weighs in neural representation. Using behavioral effect sizes from **Figure 2** pilot data to estimate the sample size required for a predicted power of 0.8 (two-tailed alpha at .05) yields a sample of N=25. This leaves open the issue of power for neural measures. Our pilot EEG data with the same task/stimuli revealed robust effects with N=23 (**Figure A**), reassuring that N=25 is a reliable target for EEG. The SNR advantages of sEEG versus EEG, and our sEEG pilot data in **Figure 3**, suggest that this sample size will be more than sufficient for sEEG measures, especially as they will be utilized in a within-patient/within-electrode experimental design.

Analyses. *Specific pre-registered analyses* will assess the hypotheses outlined in the Approach section of the proposal. Specifically, we will test the following hypotheses:

> (**H1**) broadly, the relative perceptual weight of VOT and F0, as measured behaviorally, will be reflected in cortical response, (**H2**) with modulation as a function of baseline perceptual weights, (**H3**) shifts experimentally invoked by a change in listening context by presenting speech in noise, (**H4**) and by introducing an 'accent' that shifts short-term input regularities across VOT and F0. In the latter case, our approach will allow us to test the specific directional hypothesis (**H5**) that F0 perceptual weights in the DBSL paradigm are both exaggerated by Canonical input regularities that cleanly convey a VOTxF0 correlation consistent with English and that F0 perceptual weights are down-weighted upon introduction of a regularity that violates the typical pattern of English (supported by scalp EEG pilot, **Figure A**). Our use of sEEG allows us to evaluate these hypotheses across the supratemporal plane thereby testing the strong, and falsifiable, hypothesis (**H6**) that adaptive plasticity effects are present in HG versus (**H7**) apparent only at higher levels of the cortical hierarchy. Our ability to test these hypotheses is complemented by sEEG electrode placement in cortical regions outside STP (see **Figure 3**) which will support secondary hypotheses and serve as control electrode sites.

The study design is justified our extensive behavioral research demonstrating the feasibility of the project rationale. On the electrophysiological side, our pilot data (**Figures A,3**) demonstrate the feasibility of recording robust sEEG and EEG signals responsive to the acoustic dimensions we manipulate. This will provide clear, informative, interpretable data with which to evaluate the hypotheses listed above.

Evaluating the Hypotheses: Behavioral Analyses. We will evaluate the behavioral impact of the VOT and F0 acoustic dimensions on classification using *mixed-effects logistic regression* (with patient as a random effect, stimulus VOT and F0 as fixed effects and classification responses as the outcome). Following our prior work,[14,25-29] perceptual weights for the dimensions will be computed for each patient as the correlation between dimension values and the proportion of *peach* classifications across all stimuli in the VOTxF0 stimulus grid with absolute values of the correlation coefficients normalized to sum to one as an *index of relative perceptual weight* in quiet (Aim 1) and in noise (Aim 2). To examine the impact of a change in 'accent' in the DBSL paradigm, we will use mixed logit models with responses as a function of patient, block, test stimulus F0 and the interaction between block and F0 (Aim 2). Patient will be modeled as a random effect, with the other factors as fixed effects.

Evaluating the Hypotheses: Neural Analyses. We will take a multi-pronged analysis approach. Our pilot data in **Figure 3** demonstrate that *high-γ* activity (HGA) is modulated by graded acoustic details across the VOT and F0 dimensions across electrodes placed in the STP. Following the analysis pipeline used in our pilot data analyses, we will specifically examine stimulus-time-locked HGA to the *Test* stimuli, which possess consistent, perceptually-ambiguous VOT and differentiated F0. We have specific, directional predictions (detailed above)

regarding how HGA to F0-differentiated *Test* stimuli will vary according to perceptual weight in behavior. To briefly recap, we expect that HGA to *Test* stimuli will be better differentiated (1) in the Speech-in-Noise compared to the Clear baseline context (because F0 carries greater perceptual weight); (2) in the Canonical, compared to the Reverse, context; (3) in the Canonical, compared to the Baseline Clear Speech context (because stimulus statistics exaggerate the dimension regularity in behavior).

High-gamma amplitude will be calculated using an approach that utilizes the Hilbert transform. Specifically, the signal will be filtered into 8 subbands, logarithmically spaced between 70-150 Hz. For each subband, we will calculate the amplitude (absolute value) of the analytic signal, which is estimated using the Hilbert transform. Each subband will be normalized to its baseline mean and standard deviation, estimated across trials. The HGA estimate is then the mean across these subbands.

We will use *least-squares linear regression neural encoding models* to investigate relationships between acoustic stimulus dimensions and STP neural responses during the baseline quiet context, in which stimuli sample a 2-d F0 x VOT grid. This approach will allow us to identify the subset of electrodes and temporal windows that encode at least one of these 2 dimensions at baseline; targeted analysis on this subset (described below) will then be used to compare listening contexts.

Encoding model inputs will consist of F0 and VOT, with an output of channel- and time-specific HGA. For a given electrode, individual models will be built using single trial data and a sliding window, allowing us to identify the temporal window relative to stimulus onset that yields significant models. Model quality will be assessed in two ways. First, using models built on all trials, we will calculate the regression *F*-statistic, which determines if any coefficients are significant. This will be compared to null distributions estimated with permutation tests that shuffle data across trials. Second, goodness-of-fit will be assessed for significant models by performing leave-one-out cross-validation and calculating R^2, the proportion of variance in neural activity explained by the model. Finally, we will assess the relative encoding strength of each acoustic dimension using model coefficient *t*-statistics. In summary, this approach will allow us to identify the timing and anatomical location of F0 and VOT encoding during baseline quiet listening conditions for which dimensions are sampled orthogonally (as in **Figure 1a**).

To characterize shifts in neural encoding across listening contexts, we will investigate Noise using encoding models and Canonical/Reverse contexts using *cluster-based approaches*.[32,49] Encoding models will be built from the Noise context for all channels and timepoints, using the same approach as Baseline. If a channel/timepoint is significant in either Baseline or Noise, the F0 and VOT coefficient *t*-statistics will be compared across contexts. We hypothesize that encoding of F0 will strengthen and VOT will weaken in Noise, as measured by changes in *t*-statistic magnitudes across multiple models. Next, we will compare neural responses for each of the two *Test* stimuli (which were embedded in the F0 x VOT grids, **Figure 1a**) between Baseline vs. Canonical and Canonical vs. Reverse. The clustering approach will look only at Baseline significant channels and time windows and involves randomly assigning listening context labels to single-trial data followed by a *t*-test at each time step. Across all permutations, a criterion value will be established for each timepoint (>95% of absolute value of *t*). For each of these permutations, we will next determine whether its value exceeds criterion across timepoints, and for how many timepoints it exceeds criterion (a 'cluster'). For each cluster, *t* values will be summed and assigned to all points in the cluster, with the largest summed cluster value stored for each permutation. This will create a null distribution of 1000 cluster values. We then will establish whether the cluster size calculated across real neural data (organized according to listening context) exceeds the 95% permutation-based cluster values such that $p<.001$ indicates an observed cluster is greater than all permutation-based clusters. Using this approach, we will identify context-dependent shifts in HGA responses, which we predict will reflect observed shifts in perceptual weights. Namely, we hypothesize that HGA responses in F0-encoding channels will be enhanced in the Canonical context relative to both Baseline and the Reverse context.

Rigor and Reproducibility. Analyses will be controlled for multiple comparisons, with sex as a co-variate in our analyses. We will use pre-registration and provide access to all the deidentified source data.

DISSEMINATION PLAN

The structure of this research activity is staged to meet the Specific Aims. We anticipate that work directed toward each aim will yield a major publication and with an additional paper corresponding to the collected data and the materials developed during the research program. Additionally, we anticipate 2-3 conference presentations per aim across the project period.

We will target the publications to researchers including those in cognitive neuroscience, auditory cognitive neuroscience, and speech processing. Other papers will be directed toward the neurosurgery community regarding benefits, challenges and outcomes of our work with stereoelectroencephalography (sEEG). Together the MPIs will seek to disseminate research through peer-reviewed publications, colloquium talks, and conference talks. They will be responsible for ensuring that all reportable findings are published in a peer-reviewed format in a prompt manner.

The MPIs also will endeavor to make the results broadly available to the general public supporting the work. Project personnel will be available to speak to the lay public; both the PIs have a strong history of public engagement.

The results of the studies will also be made available to the participants. This will be accomplished through lay-audience descriptions of research articles and conference proceedings on the PIs' websites and by maintaining contact with all participants (should they choose to provide their contact information). This ensures that participants are aware of the results of the studies in which they volunteered as research participants. Additionally, our publications will comply with the NIH Public Access Policy assuring the general public has access to the research they fund through their tax dollars.

Finally, we will make the data accessible through a public database as detailed in our Data Management Plan.

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

STRUCTURE OF THE STUDY TEAM

Multiple PI Leadership Plan

PI Abel and PI Holt have established an organizational structure for the conduct of all aspects of the research. Although this is a new research team, there is a clear structure that has already demonstrably produced excellent results, as exemplified by the preliminary data collected over the last year. Consistent with team-based science

PI Abel arrived in Pittsburgh, PA last year to join the Children's Hospital of Western Pennsylvania (Neurological Surgery) which is in the vicinity of Carnegie Mellon University, where PI Holt directs her laboratory. Abel and Holt have collaborated closely in developing the scientific premise and the research plan described in the proposal. The work draws synergistically from their complementary research expertise. The collaboration is supported by the geographic adjacency of their laboratories (a short drive or bus ride). Weekly joint research meetings through the Pittsburgh Cognitive Auditory Neuroscience research network and meetings specific to this project will foster continued intellectual exchange and co-mentorship of junior members of the research team. The MPIs will be involved in all scientific aspects of the proposed project; decision-making will be joint. They will collaborate to achieve the specific aims and to ensure that both data collection sites comply with US laws, DHHS and NIH policies. Both sites will have human participant research approvals to cover the scope of the proposed projects, as detailed in the sIRB Plan.

Leadership: The MPIs will oversee the project jointly, with PI Abel serving as the NIH contact who will assume, with his institution, [redacted] the fiscal and administrative management responsibilities. The MPIs will share the responsibility for the scientific direction of the research, its progress, theoretical interpretation, and dissemination. The MPIs will jointly oversee the entire Research Program, the implementation of the scientific agenda and the leadership plan as equals.

Communication: Communication among the MPIs occurs at least bi-weekly by electronic conference/phone or in person; there is more frequent contact by email, online messaging, and electronic file transfer as dictated by project demands. In these meetings, the MPIs discuss project progress, student training, experimental design, integration of the research efforts, data analysis, manuscript preparation and administrative responsibilities. Additionally, key personnel and students within the MPIs' laboratories maintain regular contact about research progress through joint lab meetings as well as through electronic data sharing, email, meet-ups at local events, and phone conversations. The MPIs will assume the responsibility for informing the other about research progress in his/her own laboratory.

Conflict Resolution: Should a conflict arise the MPIs shall meet to attempt to resolve any dispute. If this meeting fails to resolve the dispute, the appropriate Department administrators from the MPIs' home departments will attempt to settle the dispute in good faith. However, if the Department administrators fail to resolve the conflict within 30 business days, an impartial arbitration committee will be formed consisting of an impartial senior executive and a third impartial member mutually agreed upon by both the MPIs. This committee will assist in resolving the dispute. No members of the arbitration committee will be directly involved in the proposed research or in the disagreement.

Data Sharing will be open between the laboratories. The MPIs will share their respective research results with the each other, key personnel, staff and students. To facilitate data sharing, the MPIs have established a policy of electronic data sharing that serves to support the ongoing collaboration.

Publication Authorship will reflect the relative scientific contributions of the MPIs, key personnel, and students.

Any **Intellectual Property** developed as part of the proposed project will be negotiated by the Technology Transfer Offices at [redacted]Carnegie Mellon University to create a cross-institution agreement. In the event of such a negotiation, an Intellectual Property Committee of representatives from each institution will coordinate to protect intellectually property developed by the MPIs according to policies established in the agreement.

Should there be a **Change in MPI Location**, attempts will be made to transfer the relevant portion of the grant to the new institution.

A **Post-doctoral Scholar** will be involved in the research. Based at Children's Hospital, s/he will be involved in all aspects of the project, providing continuity. S/he will have full access to training in the PIs' laboratories, as well. S/he will spend time training with each PI, which will further support project continuity across sites. The post-doctoral scholar will be involved in all aspects of the work. The MPIs will work with the post-doctoral scholar to develop a post-doctoral mentoring plan, including an individual development plan. A **PhD student** based in PI Holt's laboratory will be involved in all aspects of the project, with mentoring by the senior personnel with primary responsibility by PI Holt with substantial input from PI Abel. A part-time **Clinical Research Coordinator** will assist with testing patients under the supervision of PI Abel.

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DATA SHARING PLAN

The MPIs will assume mutual responsibility for data sharing between laboratories. The research team appreciates the importance of sharing research NIH-sponsored research and will aim to make the data as widely and freely available as possible while safeguarding participant confidentiality and privacy. We seek to provide a stable, reliable and cost-effective means for distributing data, with appropriate protections for confidentiality and data longevity. Regarding the former, all data will be de-identified at the time of collection to a pre-assigned participant ID code. Data and metadata will be stored using the simplest possible formats to assure data longevity. The lowest level of individual trial-level data will be available in a de-identified format. Each type of data will be linked to detailed notes regarding how the data were generated, the metadata, and the analytical methods used to summarize and analyze them.

The MPIs will maintain the datasets privately until publication of their results. Once published, all datasets will be opened to secondary research by both internal and external collaborators. Metadata for the data sets, which includes information about the quantity of data, the domain, and research objectives (if entered by the MPIs), are always public, even if the data set is not. The data should be particularly useful for secondary analyses by multiple groups. During the project lifecycle, data set access will be restricted to the core research team. This includes the MPIs and project personnel. At the conclusion of the project, the datasets and related experimental materials will be made public and accessible through publicly available web server and/or through sources such as NeuroVault (depending on analysis type). In addition, all analysis scripts built as part of this project will be made publicly available via open source code development websites. Attracting researchers to perform secondary analysis on these data sets will occur on a lab-by-lab basis, based on presentation of works in scientific publications and professional meetings. Once published, datasets may be opened to secondary research by both internal and external collaborators by submission to data sharing websites.